STUDY ON PREVALENCE AND MANAGEMENT OF HYPERLIPIDEMIA IN FIRST-LINE RELATIVES OF PATIENTS WITH HYPERLIPIDEMIA

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ชื่อวิทยานิพนธ์ การศึกษาความชุกและการบำบัดภาวะไขมันสูงในเลือดของญาติสายตรงของผู้ป่วยที่มีภาวะไขมันสูงในเลือด

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บทคัดย่อ

วัตถุประสงค์ของการศึกษาครั้งนี้ คือ ก. เพื่อหาสาเหตุของภาวะไลโปโปรตีนสูงในเลือด ในผู้ป่วยที่มีไขมันสูงในเลือดที่มารับการรักษาที่คลินิกโภชนวิทยา โรงพยาบาลรามาธิบดี ข. เพื่อประเมินผลของการรักษาต่อระดับไขมันในเลือดและปัจจัยเสี่ยงอื่นๆ ของผู้ป่วยที่มีไขมันสูงในเลือด และ ค. ศึกษาความชุกและการบำบัดภาวะไขมันสูงในเลือดในญาติสายตรงของผู้ป่วยที่มีไขมันสูงในเลือด การศึกษาในผู้ป่วยที่มีไขมันสูงในเลือดเป็นการศึกษาย้อนหลัง ส่วนการศึกษาในญาติสายตรงเป็นการศึกษาเตรียมการล่วงหน้า ผู้ป่วยที่มีไขมันในเลือดสูงจำนวน 89 คน ประกอบด้วยผู้ชาย 30 คน และผู้หญิง 59 คน โดยมีอายุเฉลี่ย 51.0±1.2 ปี มีผู้ป่วยเพียง 25 คน เท่านั้นที่สามารถพาญาติสายตรงมาร่วมในการศึกษาครั้งนี้ ในผู้ป่วยที่มีภาวะไลโปโปรตีนสูงในเลือดชนิด IIa จำนวน 29 คน ที่ได้รับการบำบัดด้วยอาหารเป็นเวลานาน 34.8±41.3 สัปดาห์ มีระดับโคเลสเตอรอล และ low-density lipoprotein cholesterol (LDL-C) ในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยที่มีภาวะไลโปโปรตีนสูงในเลือดชนิด IIb จำนวน 8 คน ที่ได้รับการบำบัดด้วยอาหาร เป็นเวลานาน 83.2±27.8 สัปดาห์ มีเพียงระดับไตรกลีเซอไรด์ในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยที่มีภาวะไลโปโปรตีนสูงในเลือดชนิด II จำนวน 10 คน ได้รับยา bezafibrate วันละ 200-600 มก. เป็นเวลา 40.3±18.1 สัปดาห์ มีระดับโคเลสเตอรอล LDL-C และ ไตรกลีเซอไรด์ในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยที่ไลโปโปรตีนสูงในเลือด ชนิด II จำนวน 10 คน ได้รับยา gemfibrozil วันละ 600-1,200 มก. เป็นเวลา 21.9±6.5 สัปดาห์ มีระดับโคเลสเตอรอล LDL-C, high-density lipoprotein cholesterol (HDL-C) และไตรกลีเซอไรด์ในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยที่มีภาวะไลโปโปรตีนในเลือดสูง

ชนิด II ได้รับยา probucol วันละ 250-1,000 มก. เป็นเวลา 77.4±31.3 สัปดาห์ มีระดับโคเลสเตอรอล และ LDL-C ในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ ความชุกของภาวะกรดยูริกสูงในเลือด อ้วน ความดันโลหิตสูง โลหิตจาง โรคหัวใจขาดเลือด สูบบุหรี่และดื่มสุรา ในผู้ป่วยกลุ่มนี้ พบร้อยละ 68.6, 42.7, 25.8, 16.0, 11.2, 3.4 และ 2.2 ตามลำดับ จากการศึกษา พันธุประวัติพบว่า ผู้ป่วยจำนวน 15 คน เป็น familial hypercholesterolemia มี 3 คน เป็น familial combined hyperlipidemia และ 7 คน ยังไม่สามารถสรุปได้ จากจำนวนญาติสายตรงทั้งหมด 65 คน พบว่า 46 คนมีภาวะไขมันสูงในเลือด ซึ่งประกอบด้วยชนิด IIa ร้อยละ 58.5 ชนิด IIb ร้อยละ 9.2 และชนิด IV ร้อยละ 3.1 หลังจากที่ญาติสายตรงได้รับแผ่นพับซึ่งให้คำแนะนำการควบคุมอาหารเพื่อลดระดับไขมันในเลือด 8 สัปดาห์ พบว่ามีเพียง 18 คน ที่กลับมาตรวจที่คลินิกโภชนวิทยา จากการที่ระดับกรดไลโนเลอิกในซีรั่มไม่เพิ่มขึ้นที่สัปดาห์ที่ 8 ก็ชี้ให้เห็นว่า ญาติสายตรงจำนวน 18 คน นี้ไม่ได้รับประทานกรดไลโนเลอิกจากอาหารเพิ่มขึ้นซึ่งเป็นผลให้ระดับโคเลสเตอรอล และ LDL-C ในซีรั่มไม่ลดลง ญาติสายตรงที่มีภาวะไลโปโปรตีนสูงในเลือด ชนิด IIa จำนวน 7 คน ได้รับ fibric acid derivatives นาน 16 สัปดาห์ พบว่ามีระดับ โคเลสเตอรอล LDL-C ไตรกลีเซอไรด์ M และ S particle ในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ และ มี HDL-C เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ ญาติสายตรงที่มีไขมันในเลือดปกติ จำนวน 8 คน ยังคงมีระดับไขมันในเลือดปกติ หลังจากที่กลับมาตรวจอีกครั้งเมื่อครบ 1 ปี

Thesis Title Study on prevalence and management of Hyperlipidemia in first-line relatives of patients with hyperlipidemia

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ABSTRACT

The specific aims of the study are to identify the causes of hyperlipoproteinemia in the known hyperlipidemic patients attending Nutrition Clinic at Ramathibodi Hospital, to assess the effect of treatment on serum lipid levels of the known hyperlipidemic patients and the other risk factors for coronary heart disease (CHD), and to investigate the prevalence and management of hyperlipidemia in the first-line relatives of the known hyperlipidemic patients. The study in known hyperlipidemic patients was retrospective whereas the study in their first-line relatives was prospective. The 89 known hyperlipidemic patients consisted of 30 men and 59 women with the mean (±SEM) age of 51.0±1.2 yr. Only 25 patients

were able to persuade their first-line relative to participate in the study. In 29 known patients with type IIa hyperlipoproteinemia receiving dietary treatment for 34.8±41.3 wks there were significant decreases in serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels. In 8 known patients with type IIb hyperlipoproteinemia receiving dietary treatment for 83.2±27.8 wks there was significant decrease in serum triglyceride (TG) only. In 10 known patients with type II hyperlipoproteinemia receiving 200-600 mg of bezafibrate treatment daily for 40.3±18.1 wks, there were significant decreases in serum TC, LDL-C, and TG levels. In 10 known patients with type II hyperlipoproteinemia receiving 600-1,200 mg of gemfibrozil treatment daily for 21.9±6.5 wks there were decreases in serum TC, LDL-C, high-density lipoprotein cholesterol (HDL-C) and TG levels. In 13 known patients with type II hyperlipoproteinemia receiving 250-1,000 mg of probucol treatment daily for 77.4±31.3 wks, there were significant decreases in serum TC and LDL-C levels. The prevalences of hyperuricemia, obesity, hypertension, anemia, coronary heart disease, smoking, and alcohol drinking in these patients were 68.6, 42.7, 25.8, 16.0, 11.2, 3.4, and 2.2%, respectively. The pedidree study revealed 15 patients were familial hypercholesterolemia, 3 were familial combined hyperlipidemia, and 7 were inconclusive. Out of 65 first-line relatives, 46 were

hyperlipidemic: 58.5% as type IIa, 9.2% as type IIb, and 3.1% as type IV hyperlipoproteinemias. After receiving nutrition brochure, only 18 hyperlipidemic first-line relatives revisited the Nutrition Clinic 8 wk later. Since there was no increase in their serum linoleate level at week 8 this indicates that they did not increase their linoleate intake. This explains why there were no significant decreases in their serum TC and LDL-C levels at week 8. In 7 first-line relatives with type IIa hyperlipoproteinemia receiving fibric acid derivatives for 6 wk. There were significant decreases in serum TC, LDL-C, TG, M- and S-particles levels as well as significant increase in serum HDL-C levels. Eight out of 19 normolipidemic first-line relatives were still normolipidemic 1 yr later.

TABLE OF CONTENTS

PAGE

PAGE

LIST OF TABLES

LIST OF FIGURE

LIST OF ABBREVIATIONS

TC	Total cholesterol
LDL-C	Low density lipoprotein-cholesterol
HDL-C	High density lipoprotein-cholesterol
TG	Triglyceride
FV	First visit
PS	Preinitial study
IS	Initial study
CA	Corneal arcus
XA	Xanthoma
XL	Xanthelasma
EFA	Essential fatty acids
NEFA	Non-essential fatty acids
CHD	Coronary heart diseases

CHAPTER I

PROBLEMS AND OBJECTIVES

Statement of the problems

The relation between serum total cholesterol (TC) and coronary heart disease (CHD) is strong and consistent in a large number of studies and is independent of other factors. Genetic, experimental, epidemiologic, and clinical trial evidence is concordant in indicating that elevated serum TC levels due to high levels of low density lipoprotein-cholesterol (LDL-C) play a casual role in atherosclerotic heart disease (1). Clinical trials using dietary or pharmacologic intervention in population with elevated serum TC have shown the significant decrease in serum TC and LDL-C levels accompanied by the decline in the CHD incidence (2-5). Besides, there is a positive correlation between the extent to which LDL-C is lowered and the CHD incidence (6). The Lipid Research Clinic-Coronary Primary Prevention Trial (LRC-CPPT) concluded that for every 1% reduction in serum TC, there is approximately 2% decrease in the incidence of CHD events (5).

Many epidemiological studies have shown a strong inverse relation between serum high density lipoprotein-cholesterol (HDL-C) and CHD risk. Low serum HDL-C levels are often associated with lack of exercise, obesity,

cigarette smoking, and hypertriglyceridemia (5). The recent report of the Helsinki Heart Study has demonstrated the effect of gemfibrozil on the incidence of CHD in a randomized, double blind, 5 years trial in middle-aged men who were free of coronary symptoms on entry and were at high risk because of primary dyslipidemia (nonHDL-C $\geq$200 mg/dL) (7). Gemfibrozil caused a marked increase in HDL-C and persistent reduction in serum TC, LDL-C, nonHDL-C and triglyceride (TG) levels. There were minimal changes in serum lipid levels in the placebo group. The cumulative rate of cardiac end points at 5 years was 27.3 and 41.4 per 1,000 in the gemfibrozil and placebo groups, respectively. The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. The results of Helsinki Heart Study (7) agree with those of World Health Organization's study of clofibrate (4) and LRC-CPPT of cholestyramine (5) and indicate that modification of lipoprotein levels with gemfibrozil reduces the incidence of CHD in men with dyslipidemia.

Our recent study has revealed that 53% and 18% of 2,703 urban men had serum TC of 200-260 mg/dL and greater than 260 mg/dL, respectively, whereas the corresponding figures in 792 urban women were 50% and 15% (8). This signifies the existence of hypercholesterolemia in certain groups of Thai population and longitudinal study should be

carried out to establish the link between dyslipidemia and CHD in Thais (9).

Objectives and specific aims

Since hyperlipidemia is prevalent in urban Thais it is interested to investigate the causes of their hyperlipidemia. The objectives of our study are to assess the prevalence and management of hyperlipidemia in first-line relatives of patients who have already been diagnosed to be hyperlipidemia.

The specific aims of the study are

1. to identify the causes of hyperlipoproteinemia in the known hyperlipidemic patients,

2. to assess the effect of treatment on serum lipid levels of the known hyperlipidemic patients and the other risk factors for CHD, and

3. to investigate the prevalence and management of hyperlipidemia in the first-line relatives of the known hyperlipidemic patients.

The culture of fibroblast to establish the definite diagnosis of primary hyperlipoproteinemia was not carried out in this study. Thus the diagnosis of primary hyperlipoproteinemia was based on the pedigree study of the known hyperlipidemic patients which was also limited by the participation of their first-line relatives.

CHAPTER II

MATERIALS AND METHODS

Experimental design

Invitation and questionnaires were sent to 98 hyperlipidemic patients who attended Nutrition Clinic at Ramathibodi Hospital, to take part in the study on prevalence and management of hyperlipidemia in first-line relatives of patients with hyperlipidemia. Eighty-nine hyperlipidemic patients responded the questionnaires but only 25 hyperlipidemic patients were able to persuade their first-line relatives to participate in the study. Out of 235 first-line relatives, only 179 were alive and 65 attended Nutrition Clinic at Ramathibodi Hospital **(Figure 1)**.

The peried of this study covered from July 1987 to July 1988. The analysis of data in 89 known hyperlipidemic patients was retrospective based on the existing record whereas the study in 65 first-line relatives and spouses were prospective.

Criteria for the diagnosing dyslipidemia and lipoprotein phenotypes

The following criteria were used for the diagnosis of dyslipidemia: serum total cholesterol $\geq$200 mg/dL, LDL-C

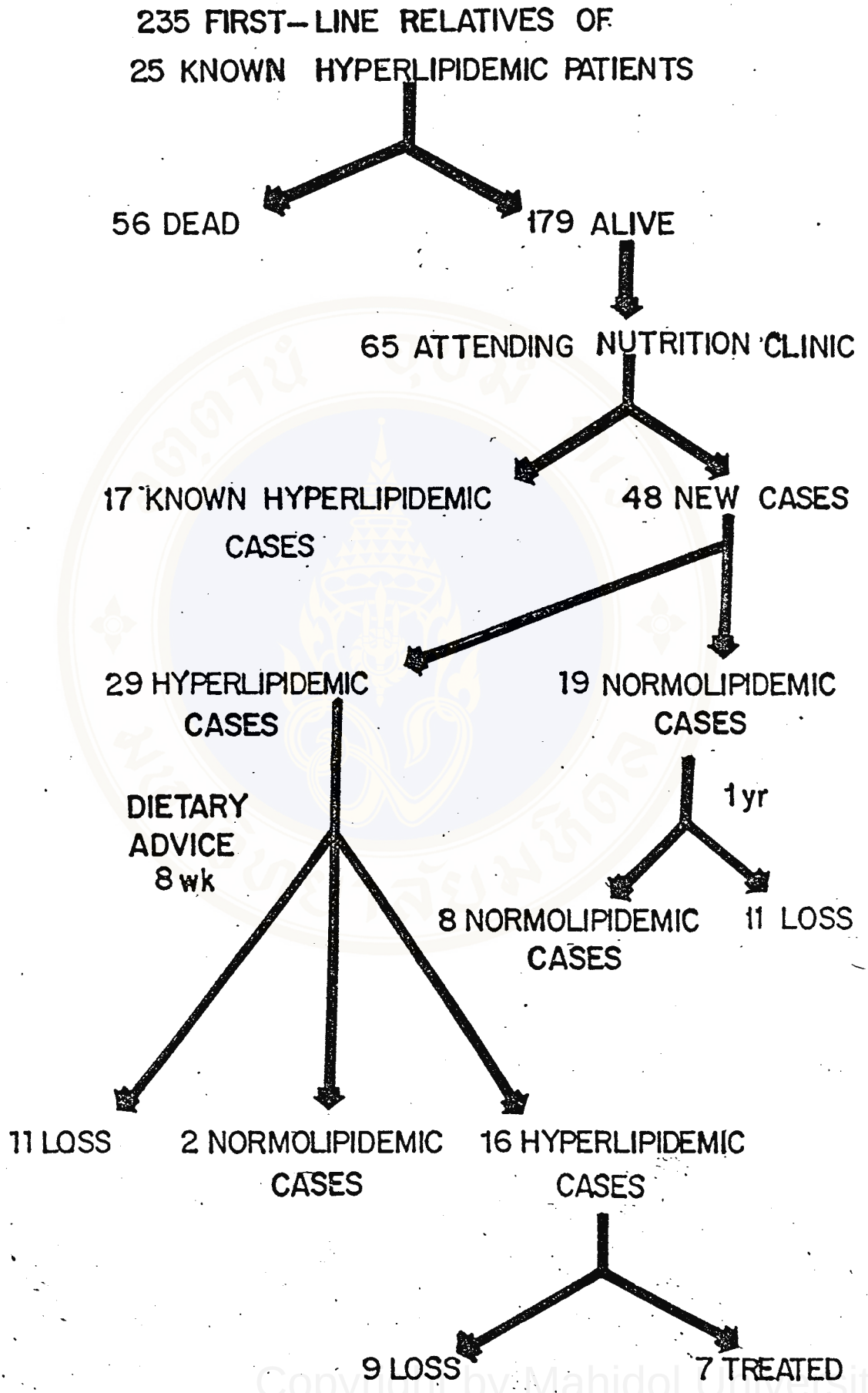

Figure 1 Study in first-line relatives

Table 1 Lipoprotein phenotypes

Lipoprotein phenotype	Cholesterol	Triglyceride	LDL-C	Chylomicron test	
				Supernatant	Infranatant
I	<260	>1000		+	-
IIa	≥200	<200	≥130	-	-
IIb	≥200	≥200	≥130	-	±
III*	350-500	350-500		-	+
IV	<200	≥200	<130	+	-
V	>300	>1000		+	+

* Presence of broad beta band by lipoprotein electrophoresis

≥130 mg/dL, HDL-C <35 mg/dL, and triglyceride ≥200 mg/dL (10,11). **Table 1** shows the criteria employed for categorizing lipoprotein phenotypes (1,10-11).

Study in 89 known hyperlipidemic patients

Questionnaires answered by 89 known hyperlipidemic patients included marital status, educational level, occupation, income, food and smoking habits, and exercise. The following informations were gathered from the patients's record: anthropometric data, hemoglobin (Hb), blood glucose, serum lipid and uric acid levels, blood pressure, presence of CHD based on electrographic finding and/or drug treatment, and physical signs suggestive of hyperlipidemia including xanthoma, corneal arcus and/or xanthelasma.

The first visit was the first time when the patients attended Nutrition Clinic at Ramathibodi Hospital. The initial study was the first time seen by the investigator of this study. The preinitial study was between the first visit and the initial study.

Study in 65 first-line relatives

Out of 65 first-line relatives, 17 had already been diagnosed to be hyperlipidemic and attended Nutrition Clinic at Ramathibodi Hospital, and 48 were new cases.

Nineteen new cases were normolipidemic and 29 new cases were hyperlipidemic (**Figure 1**).

The following parameters were carried out in the first-line relatives: dietary assessment, anthropometric measurement, inspection of physical signs suggestive of hyperlipidemia, serum lipid levels, plasma lipoprotein and fibrinogen levels, and serum fatty acid composition of total serum lipids. During the first visit all of the subjects received brochure instructing them to reduce total fat intake to 30% or less of total dietary energy, to increase linoleate intake to 10% of total dietary energy, and to reduce dietary cholesterol to less than 300 mg/day.

Normolipidemic subjects were advised for the redetermination of serum lipid levels one year later. Only 8 subjects revisited the Nutrition Clinic (**Figure 1**).

Out of 29 new hyperlipidemic cases, 18 followed the advice to attend Nutrition Clinic 8 wk later for the determination of serum lipid levels and fatty acid composition of total serum lipids. Out of 18 followed-up hyperlipidemic cases at wk 8, 16 were still hyperlipidemic. Out of 16 persistent hyperlipidemic patients, 2 were further treated with gemfibrozil, 2 received bezafibrate, and 3 were treated with fenofibrate. These 7 subjects were type IIa hyperlipoproteinemia and

followed up at 8 wk intervals. The remaining 9 subjects did not attend Nutrition Clinic **(Figure 1)**.

Study in spouses

Out of 25 known hyperlipidemic patients, 19 were married. Only 18 spouses consisting of 4 husbands and 14 wives were alive. Nine spouses were willing to participate in the study as described in the first-line relatives. The study revealed that 4 were normolipidemic and 5 were hyperlipidemic. Subsequently, only 2 hyperlipidemic spouses attended Nutrition Clinic at Ramathibodi Hospital. They were managed by dietary advice and fenofibrate.

Dietary assessment

Dietary intake was assessed in 26 first-line relatives at wk 0 by 24-hr dietary record method. The data were calculated for the total energy, protein, fat, and carbohydrate intake per caput per day as well as the percentage of energy distribution derived from protein, fat, and carbohydrate (12-14).

Anthropometric measurement

Body weight, height, triceps (TSF), biceps (BS), subscapular (SS) and suprailiac (SI) skinfold thicknesses, and mid upper arm circumference (UAC) in the subjects were

measured by using the standard technique (15). These 4 skinfold thicknesses were measured by Harpenden caliper. Standard of weight for height was based on Metropolitan Life Insurance Company (16). Body mass index (BMI) was calculated as weight in kg divided by height in m^2 (17). The mid upper arm muscle circumference (UAMC) was derived from the formula: UAMC = UAC - TSF (18). The standards of UAC, UAMC and TS were taken from the standard source (15). Percentages of body fat was estimated by the sum of the 4 skinfold thicknesses described by Durnin and Womersley (19). Waist circumference was measured at the level of umbilicus while the subject was standing and breathing normally. Hip circumference was measured at the widest point of the hip (20).

In known hyperlipidemic patients, anthropometric measurement was made at the initial study whereas in the first-line relatives and spouses the anthropometric measurement was made at 8 wk intervals.

Blood collection

Venous blood was obtained after 12-14 hr fast. Blood samples were centrifuged and serum was separated and ketp at -30 c until lipid analysis were performed. Serum lipoproteins and plasma fibrinogen were determined immediately after the separation by centrifugation of samples.

Determination of serum total cholesterol (TC)

Enzymatic-colorimetric method was used to measure serum total cholesterol by using Boehringer Mannheim Monotest Cholesterol Kit (Cat. No. 236691). The optical densities of samples and cholesterol standard were measured against reagent blank with spectrophotometer at wavelength 500 nm (21). The enzymatic reactions were as follows:

$$\text{cholesterol ester} + H_2O \xrightarrow[\text{esterase}]{\text{cholesterol}} \text{cholesterol} + RCOOH$$

$$\text{cholesterol} + O_2 \xrightarrow[\text{oxidase}]{\text{cholesterol}} \text{4-cholestenone} + H_2O_2$$

$$2H_2O_2 + \text{phenol} + \text{4-aminophenazone} \xrightarrow{\text{peroxidase}} 4H_2O + \text{4-(p-benzoquinone-monoimino)-phenazone}$$

Determination of serum high density lipoprotein-cholesterol (HDL-C)

Chylomicron, VLDL, and LDL were precipitated by adding phosphotungstic acid and magnesium chloride to the sample by the methods of Burstein (22) and Lopes-Virella (23). HDL was left in the supernatant after centrifugation and cholesterol content of HDL was determined enzymatically by the aforesaid method for total cholesterol determination.

Determination of serum triglyceride

Enzymatic hydrolysis of triglyceride (TG) with subsequent determination of the liberated glycerol by Boehringer Mannheim Triglycerides GPO-PAP Kit (Cat. No. 701912) was used to measure serum triglyceride (24). The enzymatic reactions were as follows:

$$\text{triglyceride} + 3H_2O \xrightarrow{\text{lipase}} \text{glycerol} + 3RCOOH$$

$$\text{glycerol} + ATP \xrightarrow{\text{glycerol kinase}} \text{glycerol-3-phosphate} + ADP$$

$$\text{glycerol-3-phosphate} + O_2 \xrightarrow[\text{oxidase}]{\text{glycerol phosphate}} \text{dihydroxy acetone phosphate} + H_2O_2$$

$$H_2O_2 + \text{4-aminophenazone} + \text{4-chlorophenol} \xrightarrow{\text{peroxidase}} \text{4-(p-benzoquinone-monoimino)-phenazone} + 2H_2O + HCl$$

The optical densities of sample and glycerol standard were measured against reagent blank by spectrophotometer at 500 nm.

Estimation of LDL-C concentration

LDL-C levels were calculated from Friedewald's formula (25):

LDL-C = total cholesterol - HDL-C - TG/5

Nephelometric analysis of lipoproteins

The Thorp micro-nephelometer was developed principally for the quantitative measurement of serum lipoprotein (26). The serum was diluted 10 times with physiological saline and then the light scattering intensity was read by the Thorp micro-nephelometer (LSI A). The solution was then filtered through Sartorious membrane MF 12 (Cat. No 11328) and was read again (LSI B). The response of the light scattering intensity depended upon the particle size of the suspension.

Calculation: LSI = LSI A - LSI B

1. For LSI B <50

   L-particle = LSIx0.9 mg/dL

   M-particle = (LSI B x 11.2)-58 mg/dL

   S-particle = (2.1xTC)-0.19xM-particle -10 mg/dL

2. For LSI B >50

   L-particle = LSIx0.9 mg/dL

   M-particle = (LSI B x 5.7)+210 mg/dL

   a. If TC <350

      S-particle = (2.1xTC)-0.19xM-particle -10 mg/dL

   b. If TC >350

      S-particle = (1.14xTC)-0.14xM-particle mg/dL

where, L-particle = chylomicron

M-particle = very low density lipoprotein (VLDL)

S-particle = low density lipoprotein (LDL)

TC = total cholesterol

Nephelometric measurement of plasma fibrinogen

Plasma which was separated from whole blood anticoagulated with EDTA was analyzed immediately after blood collection by diluted with 0.2% MES [2-(N-morpholino) ethane sulphonic acid)] buffered saline pH 6.3 and the light scattering intensity was read on the Thorp micronephelometer (LB). The solution was then heated in a water bath at 56 c for 15 min and was read again after cooling to room temperature (LT).

The dilution of plasma used for normal levels of fibrinogen (200-400 mg/dL) is preferably about 1/40, 1/20 dilution for lower concentration (<200 mg/dL), and 1/100 dilution for higher concentration (>400 mg/dL) (27).

Calculation: $\text{Fibrinogen (mg/dL)} = \frac{(LT-LB)xa+bx0.054}{a}$

where, a = volume of plasma

b = volume of MES-buffered saline

Analysis of serum fatty acid pattern

The analysis of serum fatty acid pattern was divided into 4 steps, i.e., extraction of total lipids,

saponification, methylation of fatty acids, and determination of fatty acid pattern by gas-liquid chromatography (GLC)

Extraction of serum lipids

Serum lipids were extracted by the method modified from Folch et al (28). 0.5 ml serum and 0.2 ml standard heptadecanoic acid (C 17:0 1 mg/ml in chloroform-methanol) were pipetted into a 15 ml glass stoppered tube. Seven ml chloroform-methanol mixture (2:1 v/v) was added and the tube was vigorously shaken. Let stand until the two phases were separated. The chloroform-methanol phase was then transferred to another glass-stoppered tube. The residue was re-extracted with 7 ml chloroform-methanol and the chloroform-methanol phase was combined together. Then 1.4 ml distilled water was added, shaken gently. Let stand until the mixture separated into two layers (about all the night). The organic phase was then transferred to reflux tube and the content was dried under nitrogen at 40 c.

Saponification

A rapid saponification technique of Ast (29) was used. Added 1 ml of 0.5 N methanolic sodium hydroxide (MSH) to the lipid residue and refluxed at 100 c for 5 min. The content was cooled in ice bath.

Methylation of fatty acids

Methylation of fatty acids was carried out by the method modified from Metcalfe et al (30). One ml of 14% BF_3-methanol (Sigma chemical Co., Ltd, St. Louis, U.S.A.) was added to the tube containing the soaps and then refluxed at 100 c for 5 minutes. The solution was cooled in ice bath and added 5 ml hexane into the sample tube. Two ml distilled water was added to the tube and shaken vigorously. Let stand until the two phases were separated and then discarded the water phase (lower part). Distilled water 4 ml was added again into the sample tube and shaken vigorously. The hexane phase was then transferred to another glass stoppered tube. The aqueous phase was reextracted with 3 ml hexane. One to two gram of anhydrous sodium sulfate was added to the combined hexane extract. The clear solution was transferred to a centrifuge tube and evaporated under nitrogen at 35 c. The fatty acid methyl esters were kept under nitrogen at -20 c until the determination was performed.

Determination of fatty acid pattern by GLC

The fatty acid methyl ester residue was dissolved with a small amount of hexane and separated by GLC (Model 5890 Hewlett Packard) with a 12 m x 0.2 mm x 0.33 m film thickness of fused-silica capillary column and a flame

ionization detector. Nitrogen was used as a carrier gas at the rate of 30 ml per minute. The column temperature was programmed from 150 c to 175 c at 3 c per minute, from 175 c to 205 c at 2 c per minute, and from 205 to 230 c at 12 c per minute with a final hold of 15 minutes. The detector temperature was 250 c.

The emergent peaks were identified by comparing their retention time with the standard fatty acid methyl esters. The relative proportion of fatty acid was derived by determining the area under each peak divided by the total area under peak of all fatty acids appeared in the chromatogram. The value was expressed as percent of total fatty acids.

Hematological parameters

Hemoglobin (Hb), packed-red cell volume (PCV), white blood cell (WBC), neutrophil and lymphocyte were measured by Hemolog 8 and Hemolog D (Technicon Instrument Corp, Tarrytown) at Clinical Pathology Laboratory, Ramathibodi Hospital.

Blood glucose, serum uric acid, liver and renal function tests, serum minerals and carbon dioxide content

Fasting blood glucose, serum urea nitrogen (SUN), creatinine, uric acid, total protein, albumin, bilirubin, alkaline phosphatase, creatine kinase, sodium, potassium,

chloride, calcium, phosphorus, magnesium, and carbon dioxide content were measured by SMA-12 at General Clinical Chemistry Laboratory, Ramathibodi Hospital.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS^{X}) on an IBM computer (31). Conventional statistical methods were used for the calculation of mean, standard errer of mean (SEM), paired or unpaired student's t-test (2-tailed), and linear regression analysis (32).

The following abbreviations were used in the legends of tables throughout this thesis.

Hyperlipidemic patients

a = significant difference from female

b = significant difference from female at the first visit

c = significant difference from female at the inital study

d = significant difference from total patients at the first visit

e = significant difference from the first visit

f = significant difference from preinitial study

g = significant difference from PS VS FV

h = significant difference from IS VS FV

First-line relatives

a = significant difference from female

b = significant difference from healthy

c = significant difference from wk 0

d = significant difference from wk 8

e = significant difference from yr 0

f = significant difference from wk 8 vs wk 0

g = significant difference from wk 16 vs wk 0

h = significant difference from wk 24 vs wk 0

i = significant difference from wk 16 vs wk 8

j = significant difference from wk 24 vs wk 8

Number 1,2,3... following the above abbreviations denoted highest to the lowest significant difference.

CHAPTER III

STUDY IN KNOWN HYPERLIPIDEMIC PATIENTS

RESULTS

Demographic data

The hyperlipidemic patients who answered the questionnaires consisted of 30 men and 59 women. **Table 2** shows their mean age when they first attended Nutrition Clinic at Ramathibodi Hospital (first visit) and when they were seen at the time of this study (initial study). **Tables 3, 4, 5, and 6** shows their marital status, educational levels, occupation, and income levels, respectively.

Dietary habit and exercise

Out of 86 hyperlipidemic patients, 68.6% had 3 meals daily **(Table 7)**. **Table 8** shows types of cooking oils consumed by 85 hyperlipidemic patients whereas **Table 9** shows favorite food consumed by 76 hyperlipidemic patients. **Table 10** shows habit of alcohol, tea, and coffee consumption in 89 hyperlipidemic patients whereas **Tables 11 and 12** show their smoking habit and exercise which was graded into regular (having exercise every day), irregular (ranging from 1 to 6 days per wk) and never.

Table 2. Age of 89 hyperlipidemic patients according to sex and lipoprotein phenotypes

Parameter	N	Mean±SEM	
		First visit	Initial study
		<---------- yr ---------->	
Sex			
Male	30	48.9±2.3	51.8±2.3
Female	59	48.6±1.4	50.6±1.4
Total	89	48.7±1.2	51.0±1.2
Lipoprotein phenotype			
IIa	55	46.2±1.8	
IIb	27	53.6±2.1	
III	1	50.0	
IV	4	48.2±4.1	
V	2	43.5 ±1.5	

Table 3. Percentages of 89 hyperlipidemic patients according to sex and marital status

Marital status	Male n=30	Female n=59	Total n=89
Single	10.0	28.8	22.5
Married	86.7	55.9	66.3
Divorced	3.3	3.4	3.4
Widow	-	11.9	7.9
Total	100	100	100

Table 4. Percentages of 88 hyperlipidemic patients according to educational levels

Educational level	Percentage of patients
Uneducated	1.1
Below primary school	27.3
Below secondary school	12.5
Secondary school	12.5
Diploma	8.0
Bachelor degree	27.3
Master degree	10.2
Doctor degree	1.1

Table 5. Percentages of 88 hyperlipidemic patients according to types of occupation

Occupation	Percentage of patients
Government official	33.0
Unemployed (the aged)	15.9
Housewife	15.9
Employee	14.8
Bussiness	14.8
Dress-maker	2.3
Laborer	2.3
Student	1.1

Table 6. Percentages of 89 hyperlipidemic patients according to income levels

Income	Percentage of patients
baht/mo.	
no income	22.5
<3000	11.2
3000-5000	14.6
5001-10000	33.7
10001-20000	15.7
20001-50000	1.1
>50000	1.1

Table 7. Number and percentages of 86 hyperlipidemic patients according to meal frequency

Meal frequency	N	%
meal/day		
2	25	29.1
3	59	68.6
>3	2	2.3

Table 8. Number and percentages of 85 hyperlipidemic patients according to types of cooking oils

Cooking oil	N	%
Lard	4	4.7
Definite types of vegetable oil	47	55.3
soybean oil	41	48.2
corn oil	2	2.4
palm olein oil	2	2.4
rice bran oil	2	2.4
Indefinite types of vegetable oils*	34	40.0

* Including soybean oil, corn oil, cottonseed oil, rice bran oil, peanut oil or palm olein oil

Table 9. Number and percentages of 76 hyperlipidemic patients according to favorite foods

Favorite food	N	%
Sweet fruits (SF)	23	30.3
Fried foods (FF)	14	18.4
Sweets (S)	3	3.9
Soft drink (SD)	2	2.6
SF+FF	11	14.5
SF+S	6	7.9
FF+S	3	3.9
S+SD	1	1.3
SF+SD	1	1.3
SF+FF+S	3	3.9
SF+FF+SD	2	2.6
SF+S+SD	1	1.3
FF+S+SD	1	1.3
SF+FF+S+SD	5	6.6

Table 10. Number and percentages of 89 hyperlipidemic patients according to alcohol, tea and coffee consumption

Beverage	Drinking					
	Never		Irregular		Regular	
	n	%	n	%	n	%
Alcohol	64	71.9	23	25.8	2	2.2
Tea	39	43.8	38	42.7	12	13.5
Coffee	31	34.8	36	40.4	22	24.7

Table 11. Number and percentages of 89 hyperlipidemic patients according to smoking habit

Smoking habit	N	%
None smoker	71	79.8
Ex-smoker	15	16.8
1-5 yr	7	
6-10 yr	3	
>11 yr	5	
Smoker*	3	3.4
1-5 yr	1	
>20 yr	2	
No. of cigarettes/day		
1-10	3	

* All of smokers are men

Table 12. Number and percentages of 89 hyperlipidemic patients according to exercise

Exercise	N	%
Regular	28	31.5
Irregular	50	56.2
Never	11	12.4

Anthropometric measurement

Table 13 shows height, body weight, and BMI in 89 hyperlipidemic patients at the first visit and initial study. In 30 male patients, there were no significant difference in body weight and BMI between the first visit and initial study. In 59 female patients, their body weight and BMI at the initial study were significantly lower than those at the first visit. Male patients were significantly taller than female patients whereas opposite results were observed for BMI. At the first visit 6.7% were underweight (BMI $\leq$20 kg/m^2) and 41.6% were obese (BMI $\geq$25 kg/m^2) (33) whereas the corresponding figures at the initial study were 7.9 and 42.7% (Table 14).

Waist and hip circumferences were measured only in 79 hyperlipidemic patients at the initial study. Male patients had significantly lower hip circumference but significantly higher waist/hip ratio than female patients (Table 15). The prevalences of abdominal obesity (waist/hip ratio >1.0 in male and >0.8 in female) in 28 male patients and 51 female patients were 7.1 and 49.0%, respectively (Table 16). Male patients had significantly lower UAC, TSF, and body fat than female patients whereas opposite result was observed for UAMC (Tables 17 and 18).

Table 13. Height, body weight and BMI in 89 hyperlipidemic patients at the first visit and initial study according to sex

Subject		Mean±SEM		
Sex	N	Height	Body weight	BMI
		cm	kg %std	kg/m^2
Male	30			
First visit		164.7±1.1 b1	64.0±1.9	111.4±2.4 b2	23.5±0.5 b2
Initial study		164.4±1.1 c1	63.5±1.9	110.3±2.4 c2	23.4±0.6 c3
Female	59			
First visit		153.4±0.6	63.1±2.0	125.6±3.2	26.7±0.8
Initial study		153.2±0.6	60.2±1.6 b1	119.7±2.4 b1	25.6±0.6 b1
Total	89			
First visit		157.2±0.8	63.4±1.5	120.8±2.4	25.6±0.6
Initial study		157.0±0.8 d2	61.3±1.2 d1	116.5±1.8 d1	24.9±0.5 d1

Significant difference from female at the first visit: b1 P<0.0001, b2 P<0.005

Significant difference from female at the initial study: c1 P<0.0001, c2 P<0.01, c3 P<0.025

Significant difference from total patients at the first visit: d1 P<0.0001, d2 P<0.05

Table 14. Prevalences of underweight, normal weight, and obesity in 89 hyperlipidemic patients at the first visit and initial study

BMI	N	Prevalence
kg/m^2		%
First visit		
<20.0	6	6.7
20.0-24.9	46	51.7
≥25.0	37	41.6
Total	89	100.0
Initial study		
<20.0	7	7.9
20.0-24.9	44	49.4
≥25.0	38	42.7
Total	89	100.0

Table 15. Waist and hip, circumferences and waist/hip ratio in 79 hyperlipidemic patients at the initial study

Subject		Circumference		Waist/hip ratio
Sex	N	Waist	Hip	
		<--------- cm -------->		
Male	28	81.3±1.8	89.5±1.1 [a1]	0.91±0.01 [a1]
Female	51	77.4±1.6	96.2±1.3	0.80±0.01

[a1] Significant difference from female: P<0.0001

Table 16. Prevalences of abdominal obesity according to sex in 79 hyperlipidemic patients at the initial study

Sex	Total patients	Prevalence*	
		N	%
Male	28	2	7.1
Female	51	25	49.0
Total	79	27	34.2

* Waist/hip ratio >1.0 in male and >0.8 in female

Table 17. Mid upper arm circumference, mid upper arm muscle circumference, and triceps skinfold thickness in 79 hyperlipidemic patients at the initial study

Subject		Mean±SEM					
Sex	N	UAC		UAMC		TSF	
		cm	%std	cm	%std	mm	%std
Male	29	28.3±0.5	96.7±1.7 a3	24.2±0.4 a1	95.5±1.6	13.3±1.2 a1	106.2±9.7 a2
Female	50	29.0±0.5	101.9±1.9	21.3±0.4	91.8±1.7	24.2±1.1	146.7±6.7
Total	79	28.8±0.4	100.0±1.4	22.4±0.3	93.2±1.2	20.2±1.0	131.8±5.9

Significant difference from female: a1 $P<0.0001$, a2 $P<0.005$, a3 $P<0.05$

Table 18. Triceps, biceps, subscapular, and suprailiac skinfold thicknesses, and body fat in 79 hyperlipidemic patients at the initial study

Subject		Mean±SEM						
Sex	N	TSF	BS	SS	SI	Sum	Body fat	
		<---------- mm ---------->					%	kg
Male	29	13.3±1.2 [a1]	6.8±0.6 [a1]	24.3±2.2	24.3±2.4	68.6±5.3 [a2]	27.8±1.3 [a1]	18.0±1.3 [a3]
Female	50	24.2±1.1	13.9±0.8	27.7±1.4	29.2±1.4	95.0±4.0	39.8±0.7	24.2±1.0
Total	79	20.2±1.0	11.3±0.7	26.4±1.2	27.4±1.3	85.3±3.5	35.4±0.9	22.0±0.9

Significant difference from female: [a1] P<0.0001, [a2] P<0.0005, [a3] P<0.001

Lipoprotein phenotypes

The majority of 89 hyperlipidemic patients were type II hyperlipoproteinemia, i.e., type IIa: 61.8% and type IIb: 30.3% (**Table 19**). **Table 20** shows their duration for attending Nutrition Clinic at Ramathibodi Hospital. **Table 21** shows mean (±SEM) serum TC, LDL-C, HDL-C, and TG levels as well as TC/HDL-C and LDL-C/HDL-C ratios in 89 hyperlipidemic patients according to lipoprotein phenotypes at the first visit. **Table 22** shows the prevalences of physical signs suggestive of hyperlipidemia in these patients at the first visit.

At the initial study there were changes of lipoprotein phenotypes from the first visit shown in **Table 23**. Fifty-nine hyperlipidemic patients at the initial study (66%) remained their lipoprotein phenotypes as the first visit.

These 89 hyperlipidemic patients were categorized into 2 groups according to dietary or drug treatment at the initial study. Thirty-nine patients received dietary treatment whereas 50 patients received drug treatment.

Table 24 shows serum lipid levels in 39 hyperlipidemic patients receiving dietary treatment at the first visit, preinitial and initial studies. At the first visit 29 patients were type IIa hyperlipoproteinemia, 8 patients were type IIb hyperlipoproteinemia, 1 patient was type III hyperlipoproteinemia, and 1 patient was type IV

Table 19. Prevalences of lipoprotein phenotypes in 89 hyperlipidemic patients according to sex at the first visit

Lipoprotein phenotype	Male		Female		Total	
	n	%	n	%	n	%
IIa	14	15.7	41	46.1	55	61.8
IIb	12	13.5	15	16.8	27	30.3
III	1	1.1	-	-	1	1.1
IV	2	2.2	2	2.2	4	4.5
V	1	1.1	1	1.1	2	2.2
Total	30	33.7	59	66.3	89	100

Table 20. Duration for attending Nutrition Clinic in 89 hyperlipidemic patients according to lipoprotein phenotypes and sex

Parameter	N	Mean±SEM
		wk
Lipoprotein phenotype		
IIa	55	126.6±19.9
IIb	27	127.4±16.1
III	1	27.0
IV	4	148.2±46.7
V	2	294.0±16.0
Sex		
Male	30	155.4±21.0
Female	59	117.8±17.4
Total	89	130.4±13.6

Table 21. Serum lipid levels in 89 hyperlipidemic patients according to lipoprotein phenotypes at the first visit

Serum lipid	Mean±SEM				
	IIa (n=55)	IIb (n=27)	III (n=1)	IV (n=4)	V (n=2)
	<---------- mg/dL ---------->				
TC	286.0±5.9	292.2±9.6	388.0	204.8±18.3	259,278
LDL-C	213.1±5.9	199.3±9.7	279.2	94.7±18.7	-
HDL-C	49.3±1.7	40.8±7.5	37.0	34.2±3.9	-
TG	118.2±5.8	261.3±8.6	359.0	346.8±58.1	1216,3124
TC/HDL-C	6.2±0.3	7.4±0.3	10.5	6.4±1.2	-
LDL-C/HDL-C	4.7±0.2	5.0±0.3	7.5	2.7±0.7	-

Table 22. Prevalences of physical signs suggestive of hyperlipidemia in 89 hyperlipidemic patients according to lipoprotein phenotypes at the first visit

Lipoprotein phenotype	CA[a]	XA[b]	XL[c]	CA+XA	CA+XL	CA+XA+XL
IIa	24.7	-	1.1	6.7	-	2.2
IIb	13.5	1.1	-	-	1.1	1.1
III	-	1.1	-	-	-	-
IV	2.2	-	-	-	-	-
V	1.1	-	-	1.1	-	-
Total	41.5	2.2	1.1	7.8	1.1	3.3

[a] CA=corneal arcus, [b] XA=xanthoma, [c] XL=xanthelasma

Table 23. Changes of lipoprotein phenotypes in 89 hyperlipidemic patients at the initial study from the first visit

First visit		Initial study					
Lipoprotein phenotype	N	IIa	IIb	III	IV	V	Normal
IIa	55	49	3	-	2	-	1
IIb	27	18	8	-	1	-	-
III	1	-	-	1	-	-	-
IV	4	1	2	-	-	-	1
V	2	1	-	-	-	1	-

Table 24. Serum lipid levels in 39 hyperlipidemic patients receiving dietary treatment at the first visit, preinitial and initial studies

Lipoprotein phenotype	Mean±SEM					
	TC	LDL-C	HDL-C	TG	TC/HDL-C	LDL-C/HDL-C
	<---------- mg/dL ---------->					
IIa (n=29)						
First visit (FV)	275.9±7.1	201.8±6.6	48.0±2.4	126.3±7.3	6.1±0.4	4.6±0.3
Preinitial study (PS)	266.6±6.9 e1,f1	193.4±6.4 e1,f1	48.8±2.4	120.8±8.6	5.8±0.4 e3,f3	4.3±0.3 e2,f1
Initial study (IS)	246.1±5.7	170.8±6.6	49.2±2.2	130.7±11.9	5.2±0.2	3.7±0.2
IIb (n=8)						
First visit	258.2±9.0	168.9±8.6	38.2±3.1	256.1±9.5	7.0±0.5	4.6±0.4
Preinitial study	236.9±15.4	151.0±13.4 f1	38.8±3.7	236.2±23.3 e4,f3	6.5±0.7	4.2±0.6
Initial study	250.6±10.2	167.4±10.0	39.6±2.0	218.4±11.7	6.4±0.3	4.3±0.3
III (n=1)						
First visit	388.0	279.2	37.0	359.0	10.5	7.5
Preinitial study	199.0	137.0	25.0	183.0	8.0	5.5
Initial study	382.0	271.6	33.0	387.0	11.6	8.2
IV (n=1)						
First visit	204.0	121.8	34.0	241.0	6.0	3.6
Preinitial study	204.0	121.8	34.0	241.0	6.0	3.6
Initial study	194.0	121.0	44.0	145.0	4.4	2.8

Significant difference from the first visit: e1 P<0.0005, e2 P<0.005, e3 P<0.01, e4 P<0.05

Significant difference from the preinitial study: f1 P<0.01, f2 P<0.025, f3 P<0.05

hyperlipoproteinemia. During the first visit and preinitial study 2 patients with type IIa and 1 patient with type III hyperlipoproteinemias received drug treatment whereas during the preinitial and initial study all of them received only dietary treatment. **Table 25** shows the duration of their dietary treatment. In type IIa and IIb hyperlipoproteinemic patients there were no significant differences in serum TC, LDL-C, HDL-C, and TG levels as well as TC/HDL-C and LDL-C/HDL-C ratios at the first visit and preinitial study. Serum TC and LDL-C levels as well as TC/HDL-C and LDL-C/HDL-C ratios in type IIa hyperlipoproteinemic patients at the initial study were significantly lower than those at the first visit and preinitial study whereas significant differences in serum TG levels were observed as the corresponding peroids in type IIb hyperlipoproteinemic patients (**Table 24**). **Table 26** shows net changes of serum lipid levels in these patients during the first visit and preinitial study, first visit and initial study as well as preinitial and initial studies.

Table 27 shows types and duration of drug treatment according to lipoprotein phenotypes. When patients with type IIa and IIb hyperlipoproteinemias were combined together and categorized according to bezafibrate, gemfibrozil or probucol they were adequate for statistical analysis.

Table 25. Duration of various subperiods in 39 hyperlipidemic patients according to lipoprotein phenotypes

Lipoprotein phenotype	N	Mean±SEM		
		FV-PS	FV-IS	PS-IS*
		<---------- wk ---------->		
IIa	29	15.7±6.3	50.4±10.7	34.8±41.3
IIb	8	4.1±2.5	83.2±27.8	79.1±27.8
III	1	23	27	4.0
IV	1	0	107	107.0

* dietary treatment

Table 26. Net changes of serum lipid levels in 39 hyperlipidemic patients on dietary treatment according to lipoprotein phenotypes

Parameter	Mean±SEM			
	TC	LDL-C	HDL-C	TG
	<---------- % ---------->			
IIa (n=29)				
PS VS FV	-2.5±2.0	-3.3±2.2	3.5±3.9	-5.2±2.8
IS VS FV	-9.7±2.1 g1	-14.1±3.1 g1	6.7±5.2	4.5±7.4
IS VS PS	-6.6±2.4	-10.0±3.6	4.1±4.3	10.4±6.9 g2
IIb (n=8)				
PS VS FV	-7.8±5.6	-9.9±7.0	0.9±3.1	-8.2±8.0
IS VS FV	-2.2±5.0	0.9±7.6	6.3±8.9	-14.0±5.4
IS VS PS	7.5±4.4	13.4±4.9	6.2±9.4	-10.6±28.1
III (n=1)				
PS VS FV	-48.7	-50.9	-32.4	-49.0
IS VS FV	-1.5	-2.5	-10.8	7.8
IS VS PS	92.0	98.5	32.0	111.5
IV (n=1)				
PS VS FV	0	0	0	0
IS VS FV	-4.9	-0.6	29.4	-39.8
IS VS PS	-4.9	-0.6	29.4	-39.8

Significant difference from PS VS FV: g1 $P<0.005$, g2 $P<0.05$

Table 27. Types and duration of drug treatment in 50 hyperlipidemic patients according to lipoprotein phenotypes

Drug	IIa		IIb		IV		V	
	n	wk	n	wk	n	wk	n	wk
Bezafibrate	7	28.4±12.7	3	68.0±57.0	3	244,7,73	1	262.0
Gemfibrozil	4	25.2±13.4	6	19.7±7.2	-	-	1	39.0
Probucol	11	85.5±36.6	2	32.5±10.5	-	-	-	-
Cholestyramine	1	27.0	4	40.8±21.8	-	-	-	-
Benfluorax	-	-	1	4.0	-	-	-	-
Fenofibrate	1	9.0	-	-	-	-	-	-
C+B	1	12.0	-	-	-	-	-	-
C+G	-	-	2	14.0±7.0	-	-	-	-
C+P	1	15.0	-	-	-	-	-	-
G+ Nicotinic acid	-	-	1	42.0	-	-	-	-
Total	26	50.2±16.7	19	32.8±9.9	3	244,7,73	2	39,262

C=Cholestyramine, B=Bezafibrate, G=Gemfibrozil, P=Probucol

Table 28 shows that serum TC, LDL-C, and TG levels as well as serum TC/HDL-C and LDL-C/HDL-C ratios at the initial study in 10 patients with type II hyperlipoproteinemia receiving bezafibrate were significantly lower than those at the first visit and preinitial study whereas the opposite result was observed for serum HDL-C level. Though their serum TC and LDL-C levels at the preinitial study were lower than those at the first visit the differences did not reach statistical significance. The mean decreases of serum TC, LDL-C, and TG levels at the initial study from the first visit were 17.7, 18.8 and 31.8%, respectively whereas the mean increases in serum HDL-C level was 29.9% (Table 29). Table 30 shows effect of gemfibrozil treatment on serum lipid levels in 10 patients with type II hyperlipoproteinemia. Only their serum TG level at the initial study was significantly lower than those at the first visit and preinitial study. Table 31 shows that the mean decreases of serum TC, LDL-C, HDL-C and TG at the initial study from the first visit were 12.2, 4.0, 4.4 and 50.0%, respectively.

Table 32 shows the effect of probucol treatment on serum lipid levels in 13 patients with type II hyperlipoproteinemia. Their serum TC and LDL-C levels at the initial study were significantly lower than those at the first visit. The mean decreases in serum TC, LDL-C, HDL-C, and TG levels at the initial study from the first

Table 28. Effect of bezafibrate treatment on serum lipid levels in 10 patients with type II hyperlipoproteinemia

Parameter	Wk	Mean±SEM					
		TC	LDL-C	HDL-C	TG	TC/HDL-C	LDL-C/HDL-C
		<---------- mg/dL ---------->					
First visit	0	296.8±12.5	222.6±14.3	44.2±2.3	150.4±34.7	6.8±0.4	5.1±0.4
Preinitial study	126.2±47.3	272.7±15.1	197.6±19.9	43.9±3.2	155.3±35.9	6.5±0.5	4.7±0.4
Initial study	40.3±18.1	249.6±8.8 e2	176.9±11.2 e2	56.2±3.0 e2,f1	81.9±11.9 e3,f3	4.6±0.4 e1,f1	3.3±0.4 e1,f2

Significant difference from the first visit: e1 P<0.005, e2 P<0.01, e3 P<0.05

Significant difference from the preinitial study: f1 P<0.005, f2 P<0.025, f3 P<0.05

Table 29. Net changes of serum lipid levels in 10 hyperlipidemic patients on bezafibrate

Parameter	Mean±SEM			
	TC	LDL-C	HDL-C	TG
	<---------- % ---------->			
PS VS FV *	-7.2±5.1	-9.3±8.8	-0.2±5.9	5.7±12.1
IS VS FV *	-14.7±4.4	-18.8±5.3	29.9±8.8 g1	-31.8±8.7 g2
IS VS PS	-5.7±6.7	-1.3±12.8	32.0±9.0 g2	-29.7±9.9

Significant difference from PS VS FV: g1 P<0.005, g2 P<0.05

Table 30. Effect of gemfibrozil treatment on serum lipid levels in 10 patients with type II hyperlipoproteinemia

Parameter	Wk	Mean±SEM					
		TC	LDL-C	HDL-C	TG	TC/HDL-C	LDL-C/HDL-C
		<---------- mg/dL ---------->					
First visit	0	279.4±10.8	189.5±11.8	45.8±2.0	220.4±21.5	6.2±0.2	4.2±0.2
Preinitial study	151.0±26.3	274.8±9.9	196.2±13.6	41.8±1.7	184.2±26.9	6.7±0.3	4.8±0.4
Initial study	21.9±6.5	243.7±16.1	179.1±17.4	42.9±2.1	107.9±13.4 el,fl	5.9±0.7	4.4±0.6

Significant difference from the first visit: el P<0.001

Significant difference from the preinitial study: fl P<0.01

Table 31. Net changes of serum lipid levels in 10 hyperlipidemic patients on gemfibrozil

Parameter	Mean±SEM			
	TC	LDL-C	HDL-C	TG
	<---------- % ---------->			
PS VS FV	-0.5±4.6	6.5±8.7	-6.9±6.4	-17.8±7.7
IS VS FV	-12.2±5.2	-4.0±7.9	-4.4±6.7	-50.0±4.1 gl
IS VS PS	-11.1±5.1	-5.8±10.3	4.1±6.7	-34.8±7.8 hl

gl Significant difference from PS VS FV: P<0.01

hl Significant difference from IS VS FV: P<0.025

Table 32. Effect of probucol treatment on serum lipid levels in 13 patients with type II hyperlipoproteinemia

Parameter	Wk	Mean±SEM					
		TC	LDL-C	HDL-C	TG	TC/HDL-C	LDL-C/HDL-C
		<---------- mg/dL ---------->					
First visit	0	296.1±15.4	219.5±16.5	54.1±4.3	127.7±17.8	5.9±0.6	4.4±0.5
Preinitial study	128.8±34.8	270.6±12.4	191.6±10.6	52.8±4.2	130.6±17.6	5.4±0.4	3.9±0.4
Initial study	77.4±31.3	251.5±8.0 e1	183.4±8.2 e2	47.9±3.2	101.6±10.6	5.6±0.5	4.1±0.5

Significant difference from the first visit: e1 P<0.01, e2 P<0.025

visit were 13.3, 12.9, 6.3 and 5.1%, respectively (**Table 33**). **Table 34** shows effect of drug treatment, regardless of types, on serum lipid levels in 50 hyperlipidemic patients according to their lipoprotein phenotypes. In 26 patients with type IIa hyperlipoproteinemia their serum TC, LDL-C, and TG levels at the initial study were significantly lower than those at the first visit. In 19 patients with type IIb hyperlipoproteinemia, their serum TC and TG levels as well as serum TC/HDL-C and LDL-C/HDL-C ratios at the initial study were significantly lower than those at the first visit and preinitial study, serum LDL-C at the initial study was significantly lower than that at the first visit, and serum HDL-C level was significantly higher than that at the preinitial study. The mean decreases in serum TC, LDL-C, HDL-C, and TG levels in patients with type IIa hyperlipoproteinemia at the initial study from the first visit were 14.0, 14.1, 6.0 and 5.8%, respectively whereas the corresponding figures in patients with type IIb hyperlipoproteinemia for serum TC, LDL-C, and TG were 17.0, 14.0 and 40.3% with the increase in serum HDL-C level of 8.6% (**Table 35**).

Prior to the initial study data on Hb, serum uric acid, blood glucose levels were available in 80 hyperlipidemic patients. **Table 36** shows that men had significantly higher Hb and serum uric acid than women.

Table 33. Net changes of serum lipid levels in 13 hyperlipidemic patients on probucol

Parameter	Mean±SEM			
	TC	LDL-C	HDL-C	TG
	<---------- % ---------->			
PS VS FV	-4.8±6.9	-5.7±8.8	-2.1±7.9	36.9±35.8
IS VS FV	-13.3±3.8	-12.9±5.2	-6.3±8.5	-5.1±25.1
IS VS PS	-3.9±7.2	-1.7±10.9	-5.4±7.1	-11.4±9.5

Table 34. Effect of drug treatment on serum lipid levels in 50 hyperlipidemic patients according to their lipoprotein phenotypes

Lipoprotein phenotype	Wk	Mean±SEM TC	LDL-C	HDL-C	TG	TC/HDL-C	LDL-C/HDL-C
		mg/dL					
IIa (n=26)							
First visit	0	298.0±9.3	226.9±9.9	50.7±2.5	109.2±9.0	6.2±0.4	4.8±0.3
Preinitial study	161.3±28.1	274.0±10.1 e2	203.4±10.8 e3	48.2±2.8	109.6±13.1 e4	6.3±0.7	4.8±0.6
Initial study	50.2±16.7	252.0±7.2	189.4±8.0	45.8±2.5	84.6±5.7	6.0±0.4	4.6±0.4
IIb (n=19)							
First visit	0	306.5±11.6	212.2±12.3	41.8±1.6	263.5±11.6 e4	7.5±0.4	5.2±0.4
Preinitial study	113.1±19.9	280.9±10.8 e2,f4	198.3±12.1 e3	38.5±1.7 f3	220.7±13.9 e1,f1	7.6±0.4 e3,f2	5.3±0.4 e4,f3
Initial study	32.8±9.9	250.3±7.5	175.7±7.6	44.2±2.3	152.0±12.2	6.0±0.5	4.3±0.4
IV (n=3)							
First visit	0	158,247,210	59, - ,103	45,27,31	270,496,380	3.5,9.1,6.8	1.3, - ,3.3
Preinitial study	42,73,47	241,144,211	159, 21,134	49,45,32	167,388,227	4.9,3.2,6.6	3.2,0.5,4.2
Initial study	244, 7,73	256,293,203	158,205,135	53,47,42	224,207,128	4.8,6.2,4.8	3.0,4.4,3.2
V (n=2)							
First visit	0	259,278	-,-	-,-	1216,3124	-,-	-,-
Preinitial study	239,48	314,202	207,-	47,-	299,777	6.7,-	4.4,-
Initial study	39,262	220,319	151,-	54,37	75,698	4.1,-	2.8,-

Significant difference from the first visit: e1 P<0.0001, e2 P<0.0005, e3 P<0.005, e4 P<0.025

Significant difference from the preinitial study: f1 P<0.0001, f2 P<0.005, f3 P<0.025, f4 P<0.05

Table 35. Net changes of serum lipid levels in 50 hyperlipidemic patients on drug treatment according to lipoprotein phenotypes

Phenotype	Mean±SEM			
	TC	LDL-C	HDL-C	TG
	<---------- % ---------->			
IIa (n=26)				
PS VS FV	- 6.1±3.9	- 7.0±5.2	- 3.2±4.8	15.9±18.8
	g3			
IS VS FV	-14.0±3.0	-14.1±3.9	- 6.0±6.1	- 5.8±13.6
IS VS PS	- 4.6±5.0	- 0.8±7.0	- 0.9±5.2	- 4.2±10.8
IIb (n=19)				
PS VS FV	- 6.4±4.5	- 2.2±7.1	- 5.6±5.5	-14.6±5.8
	g2		g2	g1
IS VS FV	-17.0±2.9	-14.0±4.5	8.6±7.1	-40.3±5.2
			g2	h1
IS VS PS	- 8.3±4.7	- 3.8±8.6	17.7±6.9	-24.9±8.8
IV (n=3)				
PS VS FV	-52.5, 41.7,-0.5	-169.5,-,-30.1	-8.9,-66.7, 3.2	38.1,21.8,40.3
IS VS FV	-62.0, -18.6,3.3	-167.8,-,-31.1	-17.8,-74.1,-35.5	17.0,58.3,66.3
IS VS PS	-6.2,-103.5,3.8	0.6,-876.2,0.7	-8.2, -4.4,-31.2	-34.1,46.7,43.6
V (n=2)				
PS VS FV	21.2,-27.3	0,0	0,0	-75.4,-75.1
IS VS FV	-15.0,-14.7	0,0	0,0	-93.8,-77.6
IS VS PS	-29.9,57.9	-27.0,0	14.9,0	-74.9,-10.2

Significant difference from PS VS FV: g1 P<0.005, g2 P<0.025, g3 P<0.05

Significant difference from IS VS FV: h1 P<0.025

Table 36. Hb, serum uric acid and blood glucose levels in 80 hyperlipidemic patients prior to the initial study

Sex	Mean±SEM					
	Hb		Uric acid		Glucose	
	N	g/dL	N	mg/dL	N	mg/dL
Male	28	15.3±0.3 [a1]	30	7.1±0.3 [a2]	30	90.0±2.2
Female	52	13.2±0.2	56	5.9±0.2	56	91.2±1.4
Total	80	14.0±0.2	86	6.3±0.2	86	90.8±1.2

Significant difference from female: [a1] P<0.0001, [a2] P<0.005

Table 37 shows that there were significant negative correlations between BMI and serum TC levels as well as between BMI and serum LDL-C levels in total patients with hyperlipidemia regardless of their lipoprotein phenotypes. In this study there were no significant correlation between BMI and serum HDL-C levels as well as BMI and serum TG levels in these hyperlipidemic patients (**Table 37**). **Table 38** shows that there was no significant correlation between serum TG and uric acid levels in 74 hyperlipidemic patients. **Table 39** shows that out of 89 hyperlipidemic patients, 59 were hyperuricemic, 38 were obese, 23 were hypertensive, 13 were anemic, 10 were CHD based on electrographic findings and/or drug treatment, 3 were smokers, and 2 were regularly alcohol drinkers.

DISCUSSION

Anthropometric measurement

In this study, the protein-calorie status in these subjects was evaluated by anthropometric measurement. According to Thomas et al (17), both % standard weight-height and BMI are the best parameters to indicate the degree of obesity. The acceptable ranges of %. standard weight-height and BMI are 90-109 % and 20-24.9 kg/m^2,

Table 37. Relationship between BMI (kg/m^2) and serum lipid levels (mg/dL) in 89 hyperlipidemic patients at the first visit

Variable	Y = a+bx	r	df	t	P
TC					
IIa	316.72-30.81x	-.1480	53	1.10	NS
IIb	346.41-54.29x	-.2145	25	1.07	NS
Total	340.32-55.38x	-.2358	87	2.31	<0.025
LDL-C					
IIa	245.98-32.80x	-.1590	53	1.18	NS
IIb	253.82-54.57x	-.2114	25	1.07	NS
Total	261.12-57.27x	-.2341	84	2.17	<0.025
HDL-C					
IIa	54.28-4.97x	-.0837	53	0.58	NS
IIb	35.87+4.96x	0.1281	25	0.66	NS
Total	53.32-7.68x	-.1349	84	1.20	NS
TG					
IIa	42.83+34.29x	0.1682	53	1.26	NS
IIb	284.05-22.60x	-.1005	25	0.51	NS
Total	238.08-15.13x	-.0100	87	0.09	NS

Table 38. Relationship between serum lipid levels (mg/dL) and serum uric acid (mg/dL) in hyperlipidemic patients

Variable (Y)	Y = a+bx	r	df	t	P
Total					
TC	266.85-0.32x	0.0098	72	-0.0830	NS
LDL	200.11-1.91x	0.0591	70	-0.4960	NS
TG	97.29+9.74x	0.1795	72	1.5480	NS
Dietary treatment					
TC	264.34+2.18x	0.0621	44	0.4130	NS
LDL	192.67+0.94x	0.0271	42	0.1760	NS
TG	122.25+7.81x	0.1239	44	0.8290	NS
Lipid lowering-drug treatment					
TC	258.44-2.32x	0.0908	26	-0.4650	NS
LDL	204.51-5.07x	0.1986	26	-1.033	NS
TG	41.96+14.96x	0.4473	26	2.5500	<0.025

Table 39. Number and percentages of associated conditions in 89 hyperlipidemic patients according to lipoprotein phenotypes

Condition	IIa		IIb		IV		V		Total	
	n	%*	n	%*	n	%*	n	%*	n	%**
Hyperuricemia**	32	37.2	21	24.4	4	4.6	2	2.3	59	68.6
Obesity	21	23.6	15	16.8	1	1.1	1	1.1	38	42.7
Hypertension	10	11.2	10	11.2	2	2.2	1	1.1	23	25.8
Anemia**	9	11.1	4	4.9	-	-	-	-	13	16.0
CHD	1	1.1	7	7.9	2	2.2	-	-	10	11.2
Smoking	1	1.1	2	2.2	-	-	-	-	3	3.4
Alcohol drinking	-	-	1	1.1	1	1.1	-	-	2	2.2

* Based on total number in each phenotype

** Based on : 86 patients for hyperuricemia and 81 patients for anemia, and 89 patients for the remaining conditions

respectively (33,34). Based on BMI, there were no striking changes in the prevalences of obesity in 89 hyperlipidemic patients between the first visit and initial study **(Table 14)**. However, female patients showed significant decreased in body weight, % standard weight-height, and BMI at the initial study from the first visit **(Table 13)**. At the initial study, complete anthropometric measurements were available in 79 hyperlipidemic patients, UAC and UAMC in male and female patients were in the acceptable ranges **(Table 17)** which indicate adequate somatic protein status.

Body density has been used as the primary measure to derive equations which relate the thickness of subcutaneous skinfolds to the body fat content. By use of Harpenden calipers, the thickness of subcutaneous fat was measured at TSF, BS, SS and SI. The amount of body fat was estimated by the sum of the 4 skinfold thicknesses described by Durnin and Womersley (19). Our female patients had more of their fat distributed subcutaneously than male patients **(Table 18)** which agrees with the study in Glaswegian adults (19).

Weight for height values shown in Fogarty table for men and women within the acceptable ranges are equivalent to an upper normal limit for the sum of the four skinfolds of 40 mm in both men and women. Total value of 60 and 80 mm are considered to be overweight and obesity, respectively. For men aged $\leq$50 yr a total value of 40,

60 and 80 mm represents body fat of 22.9, 29.2, and 33.8 % of body weight, respectively, whereas the corresponding figures for women aged ≥50 yr are 30.3, 35.7, and 39.6 % of body weight. The mean ages of our male and female patients were 51.8 and 50.6 yr **(Table 2)**. Thus based on the sum of the four skinfolds and body fat content our male patients were overweight whereas female patients were obese **(Table 18)**. The results agree with the prevalences of obesity based on BMI **(Table 14)**.

Recent Swedish analyses of the effect of different patterns of body fat distribution on mortality confirm earlier clinical observation that an abdominal rather than a gluteal distribution of fat are susceptible to the hazards of obesity including cardiovascular disease and diabetes mellitus. Therefore abdominal and hip circumferences were measured in our study **(Table 15)**. Based on a waist/hip circumference ratio of over 1 in men and over 0.8 in women for the diagnosis of abdominal obesity, our female patients had higher prevalence of abdominal obesity than male patients **(Table 16)**.

Physical signs

The majority of our hyperlipidemic patients were type II hyperlipoproteinemia **(Table 19)**. The mean period for attending our Nutrition Clinic was 130 weeks **(Table**

20). The mean serum lipid levels according to lipoprotein phenotypes at the first visit are shown in Table 21.

The physical signs suggestive of hypercholesterolemia include corneal arcus, xanthoma, and xanthelasma. These signs are commonly found in familial hypercholesterolemia (11,36).

Corneal arcus has been present in about 10% of patients with type II hyperlipoproteinemia under 30 years of age and in about 50% of patients over 30. It may be occured before the age of 10 years in homozygotes of familial hypercholesterolemia. Though corneal arcus has been observed in patients with normocholesterolemia it constitutes and independent CHD risk factors in adults under 50 years of age (36,37). In our study corneal arcus was present alone in 41.5% and in combination with xanthoma with or without xanthelasma in 11.1% of 89 hyperlipidemic patients. The majority of patients with corneal arcus were type II hyperlipoproteinemia (Table 22).

There are several kinds of xanthomas including palpebral xanthoma (xanthelasma), tendon, tuberous, planar, subperiosteal xanthomas. There are some differences in the kinds of xanthoma that occur in homozygotes and heterozygotes of familial hypercholesterolemia. Both phenotypes may have tendon xanthomas especially in the Achillis tendon and the extensor tendons

of the hand, and tuberous xanthomas, especially over the elbows. Both phenotypes also may have subperiosteal xanthomas, commonly below the knee and over the olecranon process. Soft, elevated orange-yellow planar lesions lying superficially in the skin over the extremities, buttocks, and hands are common in homozygotes and rare in the heterozygotes. Thus the occurence of xanthomas in familial hypercholesterolemia is a function of age and phenotype. The major determinants are severity and duration of the elevation in LDL, but local factors, including motion and other unknown influences, also dictate differences in the rate and location of tissue lipid deposition. Most reports show the presence of tendon xanthoma in more than half of adults with familial hypercholesterolemia and 80 percent of patients may have xanthomas before death. There is a long lag period in heteroxygotes before xanthomas usully appear. The xanthomas in homozygotes are often very severe and are sometimes present at birth. The prevalences of tendon, tuberous, and planar xanthoma, and xanthelasma in heterozygotes of familial hypercholesterolemia were 18.6, 11.1, 0.6, and 5.6%, respectively (36). In our study, the prevalences of xanthoma and xanthelasma were 13.3 and 5.5%, respectively (**Table 22**). The majority of patients with xanthoma and/or xanthelasma were type II hyperlipoproteinemia.

Effect of dietary treatment on serum lipid levels

The lowering effect of serum lipid levels resulted from low intake of dietary cholesterol and saturated fat with concomitant increase in consumption of dietary polyunsaturated fat have been shown by several studies (38-41). Shepherd et al., (42-43) studied the effect of dietary saturated and polyunsaturated fat on serum lipid levels in healthy adult men. They consumed cholesterol 400 mg/day, and 20 and 40% of total energy intake from protein and carbohydrate, respectively. The P/S ratios for saturated and unsaturated fat diets were 0.25 and 4, respectively. Compared with the saturated fat diet, the polyunsaturated fat diet significantly reduced plasma TC level by affecting the cholesterol content in VLDL, LDL, and HDL fractions. The lowered TG level was also caused by polyunsaturated fat diet.

Tanphaichitr and Pakpeankitvatana (44) studied the metabolic effects of soybean oil (SB), cotton seed oil (CS), rice bran oil (RB), and palm oil (PO) in 8 normolipidemic healthy men with age of 30-36 yr. They consumed 4 isocaloric diets each for 3 weeks. The energy distribution of each diet was 15% protein, 30% fat, and 55% carbohydrate. One-third of the fat intake came from structural fat which remained constant throughout the study. Two-thirds of the fat intake were derived from

either SB, CS, RB, or PO. The linoleate intake during the SB, CS, RB, and PO were 11.2, 11.0, 7.6 and 3.3% of total calories while the oleate and palmitate intake were 8.8 and 3.9% during the SB peroid, 7.0 and 7.0% during the CS peroid, 11.8 and 5.4% during the RB peroid, and 11.9 and 9.5% during the PO peroid. During consuming the 4 diets, the subjects had a daily cholesterol intakes of 925 mg. Serum TC and LDL-C levels were decreased by an average of 10.1 and 15.5% for SB, 7.4 and 12.0% for CS, 14.4 and 20.8% for RB, and 1.3 and 0% for PO.

PUFA representing in the human diet is essentially linoleic acid (18:2 n-6), which lowers serum cholesterol level (11). Although the lipid lowering of dietary polyunsaturated fats have found, the metabolic effects of these fats are not completely understood. In addition to their hypocholesterolemic action, polyunsaturated fats also cause reduction in plasma TG levels due to an increase in lipoprotein catabolism (45), increased excretion of neutral steroids or bile acid (46-47), alteration in the position substitution of acyl groups in plasma triglycerides (48), an increase in the proportion of PUFA in lipoprotein lipids (49) with resulting changes in the physical properties of the lipoproteins, alteration in chemical composition, thermotropic properties, and subfraction distribution of HDL without changing the fractional rate of catabolism of their major protein, apo

A-I (42), and an increase of 50% in hepatic apo B/E receptors (50).

The dietary effect in lowering serum lipid levels is also evident in our study. In 29 patients with type IIa hyperlipoproteinemia receiving only dietary treatment for 34.8±41.3 weeks **(Table 25)** there were significant decreases in serum TC and LDL-C levels as well as serum TC/HDL-C and LDL-C/HDL-C ratios **(Table 24)**. The net decreases in serum TC and LDL-C levels at the initial study from the first visit were 9.7±2.1 and 14.1±3.1%, respectively **(Table 26)**.

In 8 patients with type IIb hyperlipoproteinemia received only dietary treatment for 79.1±27.8 weeks **(Table 25)** there was significant decrease in serum TG **(Table 24)** only with a mean decrease of 14.0±5.4% **(Table 26)**. Similar finding was observed in 1 patient with type IV hyperlipoproteinemia **(Tables 24-26)**.

In 1 patient with type III hyperlipoproteinemia, his serum TC, LDL-C, HDL-C, and TG levels decreased from the initial levels after he was treated with benfluorax for 23 weeks. However, these serum lipid levels increased after stopping benfluorax for 4 weeks **(Tables 24-26)**.

Effect of drug treatment on serum lipid levels

Bezafibrate treatment Western investigators have shown the beneficial effect of bezafibrate, 2-{4-[2-(4-

chlorobenzamido)ethyl]phenoxy}-2-methyl-propionic acid, for the treatment of patients with types II, III, IV, and V hyperlipoproteinemia (51-60). Bezafibrate has the following metabolic effects: competitive inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, inhibition of acetyl coenzyme A reductase, activation of hepatic and extrahepatic lipoprotein lipase, increased -oxidation of fatty acids, and increase LDL receptor-dependent catabolism (11). Thus bezafibrate lowers increased serum TC and TG levels in various phenotypes of hyperlipoproteinemia (51-60). The VLDL-and LDL-lowering action of bezafibrate brings about a reduction in the serum lipid level of 29-48% for TG and 15-22% for TC. It has been shown that patient with hyperlipoproteinemia treated daily with 600 mg of bezafibrate for 12 mo, degree of reduction in serum TC and TG depends on lipoprotein phenotypes. In type IIa hyperlipoproteinemia, the reduction in serum TC is predominant: 20% reduction in serum TC and 37% reduction in serum TG. In type IIb hyperlipoproteinemia, in addition to the decrease in serum TC serum TG is markedly reduced: 16% reduction in serum TC and 50% reduction in serum TG. Tanphaichitr et al.,(61) have shown that 8 patients with type II hyperlipoproteinemia treated with 600 mg of bezafibrate for 24 weeks had 12-31% reduction in serum TC and 35-48% reduction in serum TG. Our retrospective study in 10

patients with type II hyperlipoproteinemia receiving 200-600 mg of bezafibrate treatment daily for 40.3±18.1 weeks showed significant decreases in serum TC, LDL-C, and TG levels **(Table 28)**. The mean (±SEM) decreases in these serum lipid levels were 14.7±4.4, 18.8±5.3 and 31.8±8.7%, respectively **(Table 29)**.

The HDL-C increase observed in most studies with bezafibrate is not merely a reflection of the VLDL decrease, since no significant correlation could be found between the changes in the two parameters (62). Schwandt and Weisweiler (63) have shown that the HDL-C increase is due to a rise of HDL_2-fraction. In the report of Tanphaichitr et al., (61) there were no significant changes in serum HDL-C levels during the study. However, our study showed significant increase in serum HDL-C level **(Table 28)**. The mean(±SEM) increase in serum HDL-C level was 29.9±8.8% **(Table 29)**.

Gemfibrozil treatment A number of clinical studied have shown a beneficial effect of gemfibrozil, 5-(2,5-dimethylphenoxy)-2, 2-dimethylpentanoic acid, on serum TC and TG levels, and on cholesterol concentrations of VLDL, LDL, and HDL (64-69).

Gemfibrozil is well absorbed after oral administration with the peak plasma levels of 1-2 hr after ingestion. Its plasma half-life is approximately 1.5 hr. It matabolizes of oxidation of the ring methyl group.

Seventy percent of gemfibrozil is excreted unchanged in urine and 6% is excreted in feces (70). Clinical studies have shown that gemfibrozil lowers serum TC, LDL-C, VLDL-C, and serum TG levels but raises HDL-C level (64-69).

Animal studies suggest that gemfibrozil inhibits the incorporation of long-chain fatty acids into newly formed TG and, likewise, inhibits basal adipose tissue lipolysis (71-72). Study in patients with primary hypertriglyceridemia has shown that gemfibrozil lowers TG by decreasing VLDL synthesis and by accelerating the catabolism of VLDL by increasing the amount of extrahepatic lipoprotein lipase and VLDL apoprotein CII : CIII ratio. It increases plasma HDL levels by stimulating synthesis of apoproteins AI and AII. A suppression of hepatic TG lipase may also contribute towards increased HDL (70).

The average magnitude of change in serum lipoprotein level after gemfibrozil treatment is fairly variable from patient to patient (70). In type IIa patients, gemfibrozil 1,200 mg/day for 3 mo. results in a 22% reduction in serum TC, 28% reduction in LDL-C, 40% reduction in serum TG, 38% reduction in VLDL, and 6% increase in HDL-C. In type IIb patients it decreases serum TC 18%, LDL-C 19%, serum TG 50%, and VLDL 49%, but increases HDL-C 15% (73).

Tanphaichitr et al., (74) have shown the efficacy of gemfibrozil for the treatment of patients with types IIa and IIb hyperlipoproteinemia. This is evidenced by the significant decreases in serum TC, LDL-C, and TG as well as plasma M-and S-particle levels during an 8-wk gemfibrozil treatment, as well as significant increases of the aforesaid parameters after stopping gemfibrozil treatment for 4 wk. In their 8 patients with type IIa hyperlipoproteinemia, the net changes of serum lipid levels were as follows: serum TC -17%, LDL-C -33%, TG -35%, and HDL-C +13%, whereas the corresponding figures in 6 patients with type IIb hyperlipoproteinemia were -25, -27, -60, and +11%, respectively. Our retrospective study in 10 patietns with type II hyperlipoproteinemia receiving 600-1,200 mg of gemfibrozil treatment daily for 21.9±6.5 weeks showed decreases in serum TC, LDL-C, HDL-C, and TG levels. However, significant difference was observed for serum TG only **(Table 30)**. The mean (±SEM) decrease in serum TG was 50.0±4.1% **(Table 31)**.

Probucol treatment Probucol is a sulfur-containing butylphenol compound, i.e., 4, 4'-(isopropylidenedithio) bis(2,6-di-t-butylphenol). It is absorbed to the portal circulation and appears to exert its primary action by inhibiting cholesterol biosynthesis. The drug also acts to enhance the synthesis and excretion of bile acids (75-77). Probucol usually reduces serum TC levels of patients

with type II hyperlipoproteinemia by 10-20% from the average baseline values. Tanphaichitr and Banphotkasem (78) treated 18 patients with type II hyperlipoproteinemia with 500 mg of probucol given orally twice a day for 24 wk. The patients were also intructed to increase their linoleate intake during the study. Their mean(±SEM) serum TC, LDL-C, HDL-C and TG levels at wk 0 were 311±11, 239±10, 41±3 and 157±19 mg/dL, respectively. After receiving probucol treatment, there were significant decreases in serum TC and LDL-C levels. Their mean(±SEM) serum TC levels at wk 4, 8, 12, 16, 20 and 24 were 234±15, 245±16, 225±12, 221±13, 226±15 and 229±13 ma/dL whereas serum LDL-C at the corresponding periods were 174±18, 177±21, 166±14, 168±15, 171±17 and 171±16 me/dL. The decreases of serum TC levels during weeks 4-24 ranged from 21-29%. The decrease in serum HDL-C levels after probucol treatment in their patients is consistent with previous reports (75). This effect has caused some concern because HDL is believed to have an antiatherogenic effect. However, several studied have shown that long-term administration of probucol has resulted in regression of cutaneous and tendinous xanthoma (79) and in a suggestive reduction of clinical cardiovascular events (80-81). Our retrospective study in 13 patients with type II hyperlipoproteinemia receiving 250-1,000 mg of probucol treatment daily for 77.4±31.3 weeks showed significant

decreases in serum TC and LDL-C levels. Their serum TG and HDL-C levels tended to decline but did not reach statistical significance **(Table 32)**. The mean(±SEM) decreases in serum TC, LDL-C, HDL-C, and TG were -13.3±3.8, -12.9±5.2, -6.3±8.5, and -5.1±25.1%, respectively **(Table 33)**. Since probucol does not affect VLDL (75) this explains why there were no significant changes in serum TG levels in our patients during probucol treatment (77,82).

Various drug treatment We had evaluated the effect of various drug treatment on serum lipid levels in 50 hyperlipidemic patients consisting of 26 patients with type IIa, 19 patients with type IIb, 3 patients with type IV, and 2 patients with type V hyperlipoproteinemias **(Table 27)**. Both type IIa and IIb hyperlipoproteinemic patients receiving various types of hypolipidemic drugs had significantly decreased in serum TC, LDL-C, and TG levels. Only the latter group showed significant increase in serum HDL-C level. The mean(±SEM) decreases in serum TC, LDL-C, and TG after receiving the treatment for 50.2±16.7 weeks were 14.0±3.0, 14.1±3.9 and 5.8±13.6%, respectively for type IIa hyperlipoproteinemic patients and for 32.8±9.9 weeks were 17.0±2.9, 14.0±4.5 and 40.3±5.2%, respectively for type IIb hyperlipoproteinemic patients. The mean(±SEM) increase in serum HDL-C level in the latter group was 8.6±7.1% **(Table 35)**.

All of the 3 patients with type IV hyperlipoproteinemia were treated with bezafibrate **(Table 27)**. All of them exhibited decreases in serum TG levels with concomitant increases in serum HDL-C levels. However, serum TC levels in 2 patients increased **(Tables 34 and 35)**. One patient with type V hyperlipoproteinemia was treated with bezafibrate whereas the other was treated with gemfibrozil in addition to restriction of total fat intake. Serum TG level in the patient on bezafibrate became normal with concomitant decrease in serum TC level whereas serum TG level in the patient on gemfibrozil was still higher than the normal level **(Tables 34 and 35)**. However, the initial serum TG level in the latter patient was higher than the former.

Associated condition

Though obesity is not related to the development of CHD directly plays a central role in the constellation of cardiovascular risk factors by which the risk of developing hypertension, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, low serum HDL-C level (11,83-85). However, in our study there were low significant negative correlations between BMI and serum TC levels as well as between BMI and serum LDL-C levels **(Table 37)**. It should be noted that this correlations were not observed

when the relationship was analyzed according to lipoprotein phenotypes.

The rate of CHD death in men with high diastolic blood pressure was 79%, higher than in men with normal diastolic blood pressure (≤90 mmHg) (86). Risk of some categories of CHD, e.g., coronary insufficiency and sudden death are increased almost 50% by borderline hypertension (140-159/90-94 mmHg) (87). There is a progressive increase in risk of CHD with increasing of both systolic and diastolic blood pressure, even more so in the presence of multiple risk factors such as hypercholesterolemia, hyperglycemia, and cigarette smoking (88). The actual mechanisms by which hypertension accelerates atherosclerosis vascular disease are unknown. It is thought that hypertension may lead to smooth muscle cell proliferation with medial thickening and most importantly, to an increase in the arterial wall content of elastin, collagen, and glycosaminoglycan. Such an effect would be mediated by platelet-derived growth factor (PDGF) (89).

Cigarette smoking is associated with CHD and the risk increases with number of cigarettes smoked per day (90). The two major cigarette components that are identified as noxious effect to the cardiovascular system are nicotine and carbon monoxide. Nicotine stimulates catecholamine release, increases myocardial irritability

and heart rate, causes vascular constriction and a transient rise in blood pressure, causes injury to the arterial wall, increases platelets adherence, and causes the releasing of PDGF. Carbon monoxide, furthermore may exert its adverse influence through vascular toxic and inflammatory effects, homostatic changes, and accelerated atherosclerosis, and it can also worsen the situation by reducing the oxygen available, hypoxia to the myocardium and HDL-C level (90-91).

Some investigators consider hyperuricemia as a risk factor of CHD. Serum uric acid level is also influenced by obesity and hypertriglyceridemia (92). Significant positive correlation between serum TG and uric acid levels was observed in our patients receiving hypolipidemic drugs **(Table 38)**.

None of the 89 hyperlipidemic patients was diabetes mellitus. Their mean blood glucose level prior to the initial study was within normal limit. Male patients had significantly higher hemoglobin and serum uric acid levels than female patients **(Table 36)**. This is consistent with the existing knowledge. The prevalences of hyperuricemia, obesity, hypertension, anemia, CHD, smoking, and alcohol drinking in these patients were 68.6, 42.7, 25.8, 16.0, 11.2, 3.4, and 2.2%, respectively **(Table 39)**. These associated conditions may increase the risk for the development of CHD.

CHAPTER IV

STUDY IN FIRST-LINE RELATIVES AND SPOUSES

RESULTS

The results were divided into 5 parts: baseline data in 65 first-line relatives, effect of dietary advice on lipid status in 18 first-line relatives with hyperlipidemia, effect of drug treatment in 7 first-line relatives with hyperlipidemia, 1 yr follow-up in 8 normolipidemic first-line relatives, and study in 9 spouses.

Baseline data in 65 first-line relatives

Clinical data, serum lipid levels, and pedigrees of 25 known hyperlipidemic patients

Table 40 shows number, percentages and ages of the participating first-line relatives and spouses of 25 known hyperlipidemic patients. **Tables 41-43** show clinical and serum lipid data in 65 first-line relatives and 9 spouses of 25 known patients with hyperlipidemia whereas **Figures 2-7** show pedigrees of their families.

Dietary assessment

Dietary assessment was carried out in 26 out of 48 new cases of first-line relatives. **Table 44** shows their

Table 40. Number, percentages and ages of the participating first-line relatives and spouses of 25 known hyperlipidemic patients

Relative	No.		Participation		Mean±SEM
	Dead	Alive	No.	%*	Age
Father	19	6	2	33.3	52,62
Mother	17	8	2	25.0	58,61
Siblings	20	108	21	19.4	47.1±3.5
Male	12	52	10	19.2	42.3±5.3
Female	8	56	11	19.6	51.5±4.4
Son	-	30	17	56.7	21.5±2.1
Daughter	-	27	23	85.2	22.5±1.7
Spouse	2	18	9	50.0	49.0±2.9
Total**	56	179	65	36.3	-

* Based on alive relatives and excluding spouses

** Excluding sponses

Table 41. Clinical and serum lipid data in family members of 14 known patients with type IIa hyperlipoproteinemia

Family	Case no.	Sex	Age	TC	TG	LDL-c	HDL-c	Sign a CA	Sign b XA	Sign c XL	Type	Associated disease
			yr.	<----- mg/dL ------->								
VS.	1	M	24	309	86	263	29	+	+		IIa	
	2	M	26	368	76	316	37		+		IIa	
	3	M	52	423	143	368	29	+	+		IIa	
TS.	1	F	27	317	101	242	55	+			IIa	
	2	F	29	253	59	206	35		+	+	IIa	
SV.	1	M	48	223	181	144	43	+			IIa	
	2	F	42	295	133	221	47				IIa	
	3	F	16	172	60	122	38				N	
	4	F	13	163	141	101	33				N	
AM.	1	M	44	242	125	178	39	+			IIa	
	2	F	43	178	89	117	44				N	
	3	M	15	134	69	66	54				N	
	4	M	12	131	90	72	41				N	
	5	F	6	140	66	88	39				N	
CP.	1	F	45	362	110	271	69	+	+		IIa	
	2	M	19	278	100	221	37				IIa	
BY.	1	F	25	342	70	280	48	+			IIa	
	2	F	39	391	115	335	33	+	+		IIa	
	3	M	21	168	85	98	53				N	
	4	F	58	345	179	272	36	+	+		IIa	HT
PV.	1	M	37	306	55	250	45	+			IIa	
	2	M	33	259	144	185	45	+			IIa	
	3	M	31	236	133	164	45	+			IIa	
	4	M	30	278	236	186	45	+			IIb	
KK.	1	M	41	420	115	352	45	+	+	+	IIa	
	2	F	37	190	72	118	58				N	
	3	F	61	361	147	287	45	+	+		IIa	CHD
	4	M	14	226	80	158	51				IIa	
	5	M	10	499	86	424	56				IIa	
KA.	1	M	49	365	101	300	45	+	+	+	IIa	
	2	F	48	248	65	160	76				IIa	
	3	F	22	190	67	119	58				N	
RC.	1	F	55	307	103	218	68	+			IIa	
	2	M	55	264	163	196	35	+			IIa	
	3	F	18	205	59	144	49				IIa	
OR.	1	F	34	297	154	221	45	+			IIa	
	2	F	35	337	199	225	72	+			IIa	
	3	M	62	287	280	193	38	+			IIb	
SD.	1	M	33	270	193	189	42				IIa	
	2	F	35	246	200	161	45				IIb	
SK.	1	F	62	213	122	153	36				IIa	
	2	F	67	223	157	138	54				IIa	HT
	3	F	32	275	207	157	76				IIb	
	4	F	31	289	350	176	43				IIb	
JB.	1	F	50	347	175	252	60		+	+	IIa	
	2	F	51	202	254	110	41				IV	

a Corneal arcus; b xanthoma; c xanthelasma

Table 42. Clinical and serum lipid data in family members of 8 known patients with type IIb hyperlipoproteinemia

Family	Case no.	Sex	Age	TC	TG	LDL-c	HDL-c	Sign a CA	Sign b XA	Sign c XL	Type	Associated disease
			yr.	<----- mg/dL -------->								
TT.	1	M	59	353	216	245	45	+	+	+	IIb	
	2	M	21	225	112	162	40				IIa	
	3	M	20	253	126	187	41				IIa	
	4	F	19	233	67	174	45				IIa	
PS.	1	M	69	296	376	176	45	+			IIb	ET
	2	F	59	277	117	187	67	+			IIa	
	3	F	38	231	90	155	57				IIa	
	4	M	34	299	135	216	57	+			IIa	
JR.	1	M	68	314	222	225	44	+			IIb	
	2	F	65	269	142	185	55	+			IIa	ET
	3	F	63	277	116	194	60	+			IIa	
	4	F	64	276	172	199	43				IIa	CHD
	5	M	34	278	67	200	65				IIa	
	6	F	32	230	48	158	62				IIa	
	7	M	30	221	54	159	52				IIa	
TV.	1	M	72	303	257	216	36	+			IIb	
	2	F	70	251	110	210	29				IIa	
	3	M	67	459	219	369	46	+			IIa	
	4	M	65	296	109	228	46	+			IIa	ET
PP.	1	F	57	278	253	193	34	+			IIb	
	2	F	28	253	108	170	61				IIa	
	3	F	24	199	70	131	54				N	
	4	M	23	180	74	115	50				N	
MT.	1	M	45	248	342	141	39				IIb	CHD
	2	F	24	173	91	115	40				N	
	3	F	23	166	67	105	48				N	
	4	F	19	127	49	60	58				N	
	5	F	13	220	132	140	54				IIa	
	6	F	17	251	160	171	48				IIa	
	7	M	15	129	82	75	38				N	
AP.	1	M	48	340	253	244	45				IIb	CHD, HT
	2	M	60	201	180	122	43	+			IIa	DM, HT
	3	F	54	206	137	138	40	+		+	IIa	HT
	4	M	49	212	252	128	34	+			IV	DM
	5	M	41	196	145	128	39				N	DM
SS.	1	M	52	236	276	149	32				IIb	CHD
	2	M	19	150	102	96	33				N	

a Corneal arcus; b xanthoma; c xanthelasma

Table 43. Clinical and serum lipid data in family members of 3 known patients with type IV hyperlipoproteinemia

Family	Case no.	Sex	Age	TC	TG	LDL-c	HDL-c	Sign a CA	Sign b XA	Sign c XL	Type	Associated disease
			yr.	<----- mg/dL -------->								
KT.	1*	M	57	158	270	59	45	+			IV	HT,CHD
	2	F	59	272	163	184	55	+			IIa	
	3	F	48	189	75	130	44				N	
	4	F	20	164	78	94	54				N	
	5	F	17	211	80	134	61				IIa	
	6	F	15	157	88	92	48				N	
VN.	1	M	46	210	380	103	31				IV	
	2	F	45	192	140	124	40				N	
	3	M	16	165	58	98	55				N	
	4	M	14	183	79	115	52				N	
PD.	1	F	60	247	496	-	27	+			IV	CHD
	2	M	38	270	156	203	35				IIa	
	3	F	35	217	62	166	39				IIa	
	4	F	33	233	74	179	40				IIa	
	5	M	31	256	75	191	50				IIa	
	6	F	22	202	84	150	35				IIa	

* Treated with clofibrate

a Corneal arcus; b xanthoma; c xanthelasma

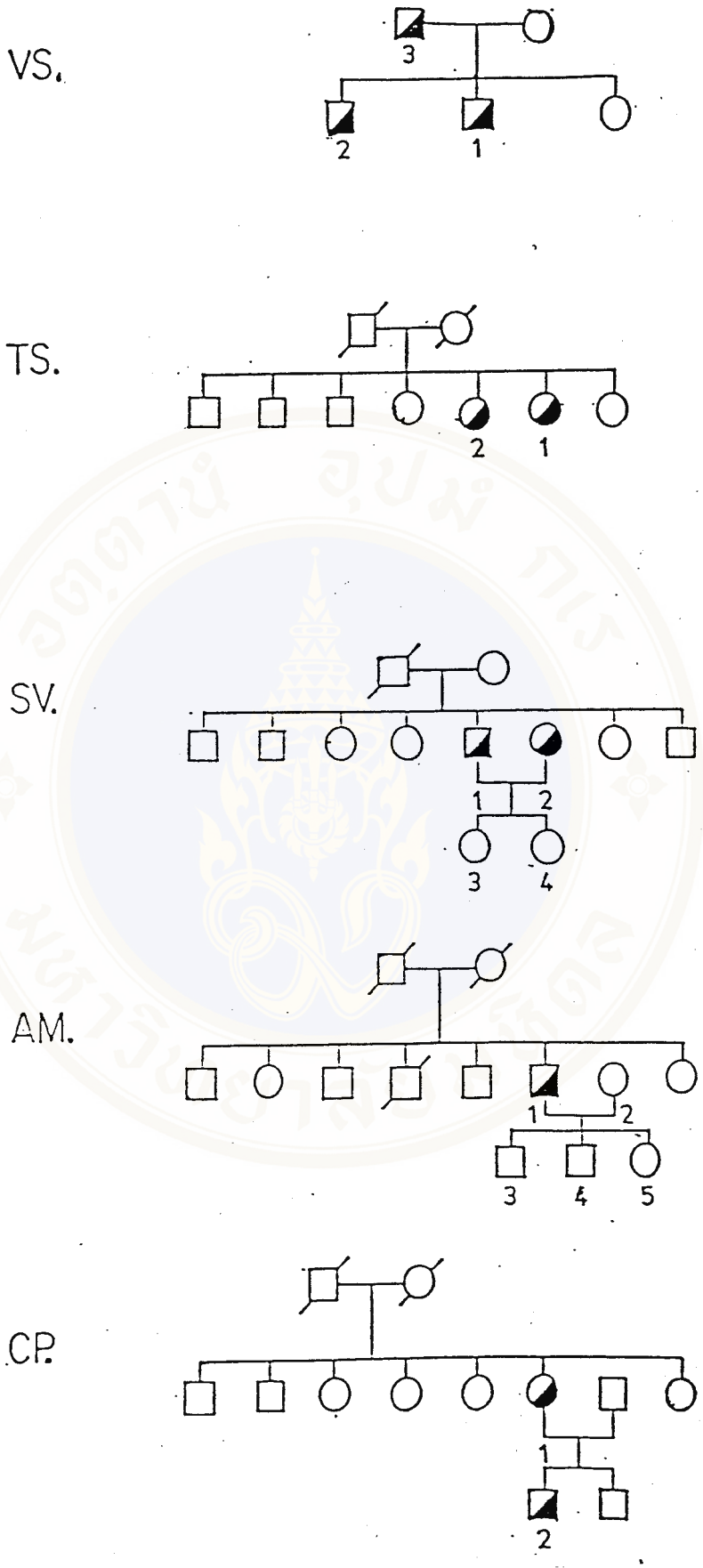

Figure 2. Pedigrees of families VS, TS, SV, AM and CP. Case numbers are subjects attending Nutrition Clinic and correspond to Table 41. □ : male ○ : female

□○ : dead person ◪◓ : hypercholesterolemia.

□○ : normolipidemia.

NO NO

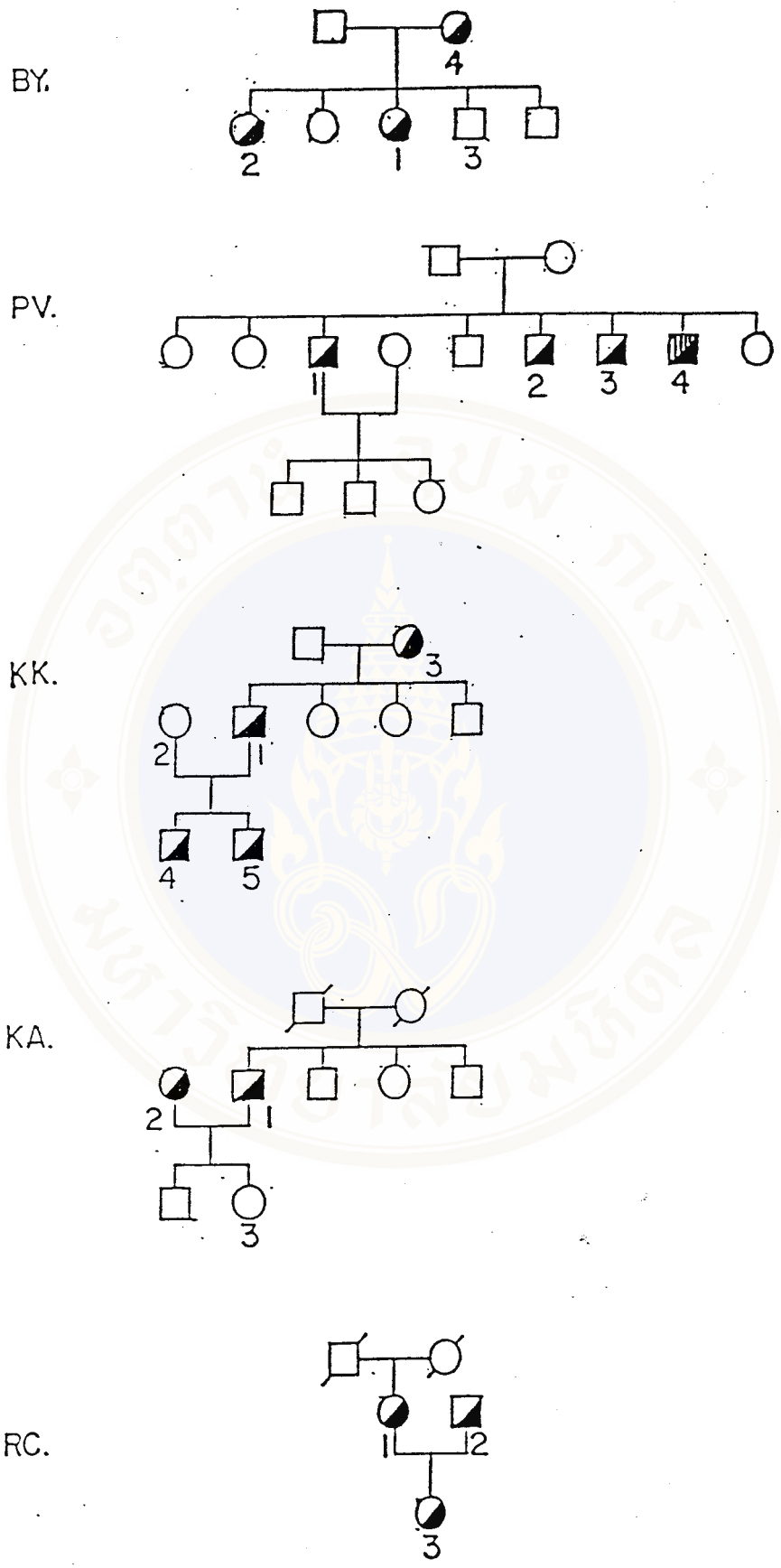

Figure 3. Pedigrees of families BY, PV, KK, KA and RC. Case numbers are subjects attending Nutrition Clinic and correspond to Table 41. ▨ ⓟ ; hypertriglyceridemia. See legend of Figure 2 for other symbols.

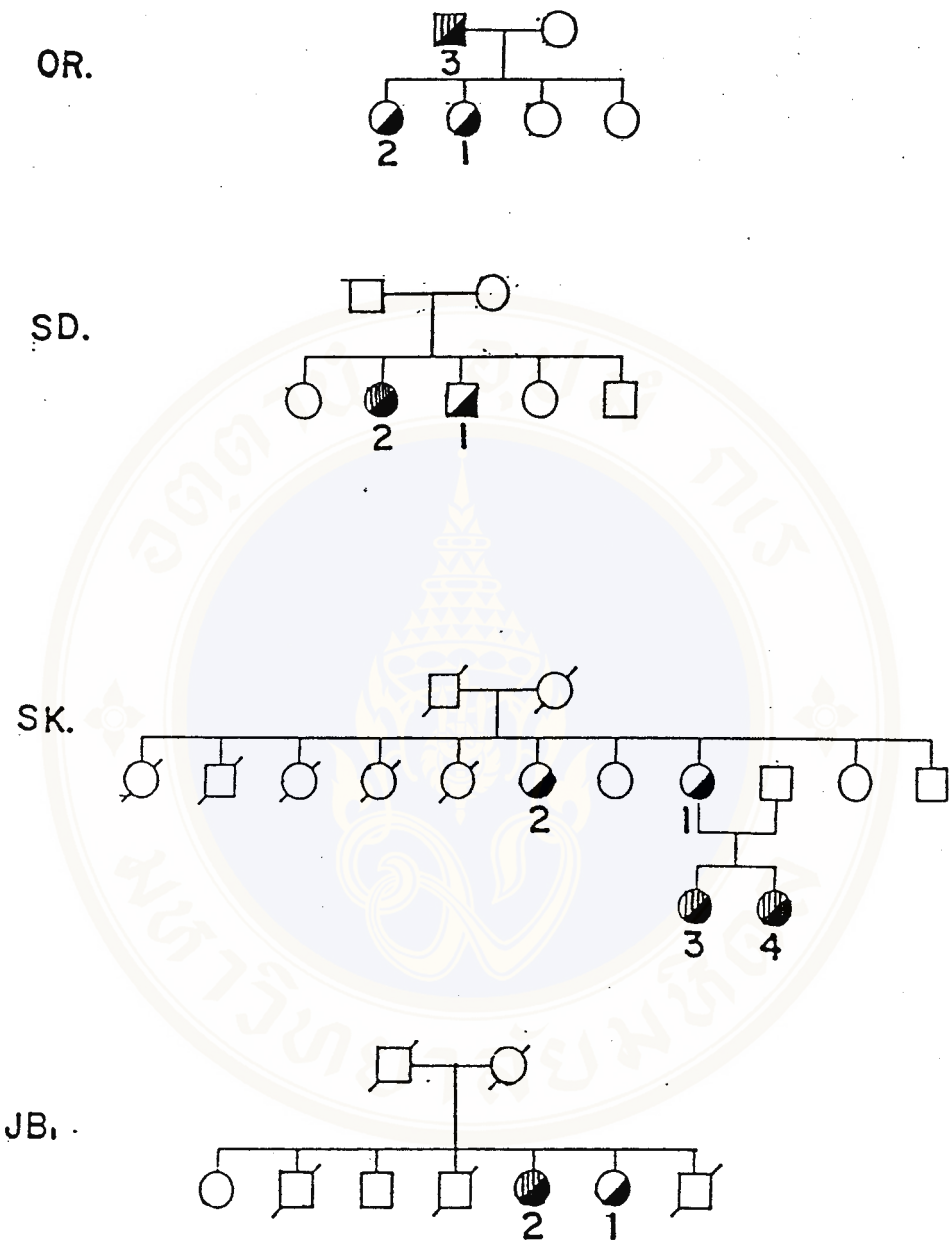

Figure 4. Pedigrees of families OR, SD, SK, and JB. Case numbers are subjects attending Nutrition Clinic and correspond to Table 41. See legends of Figure 2 and 3 for the explanation of symbols.

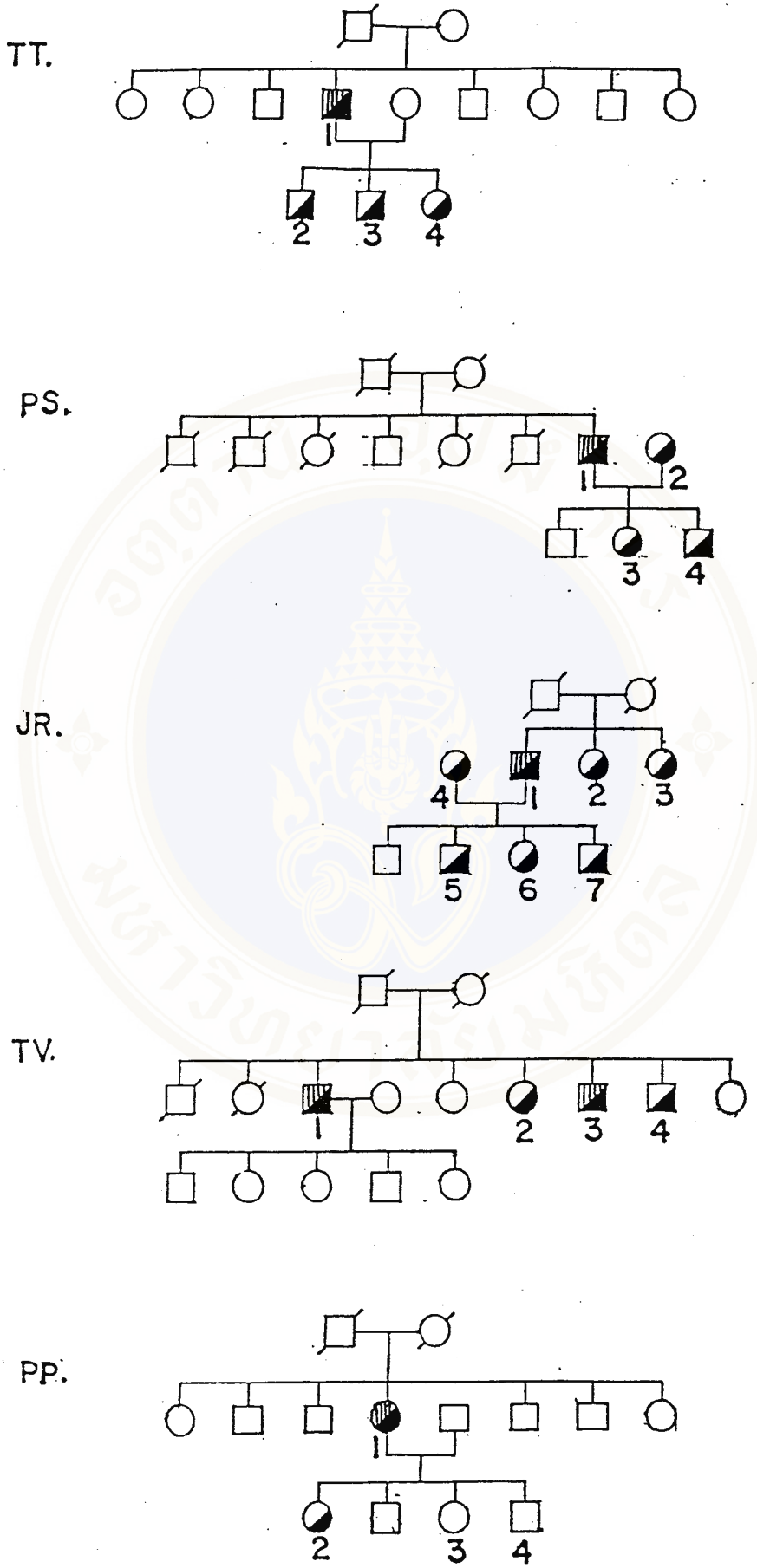

Figure 5. Pedigrees of families TT, PS, JR, TV and PP. Case numbers are subjects attending Nutrition Clinic and correspond to Table 42. See legends of Figure 2 and 3 for the explanation of symbols.

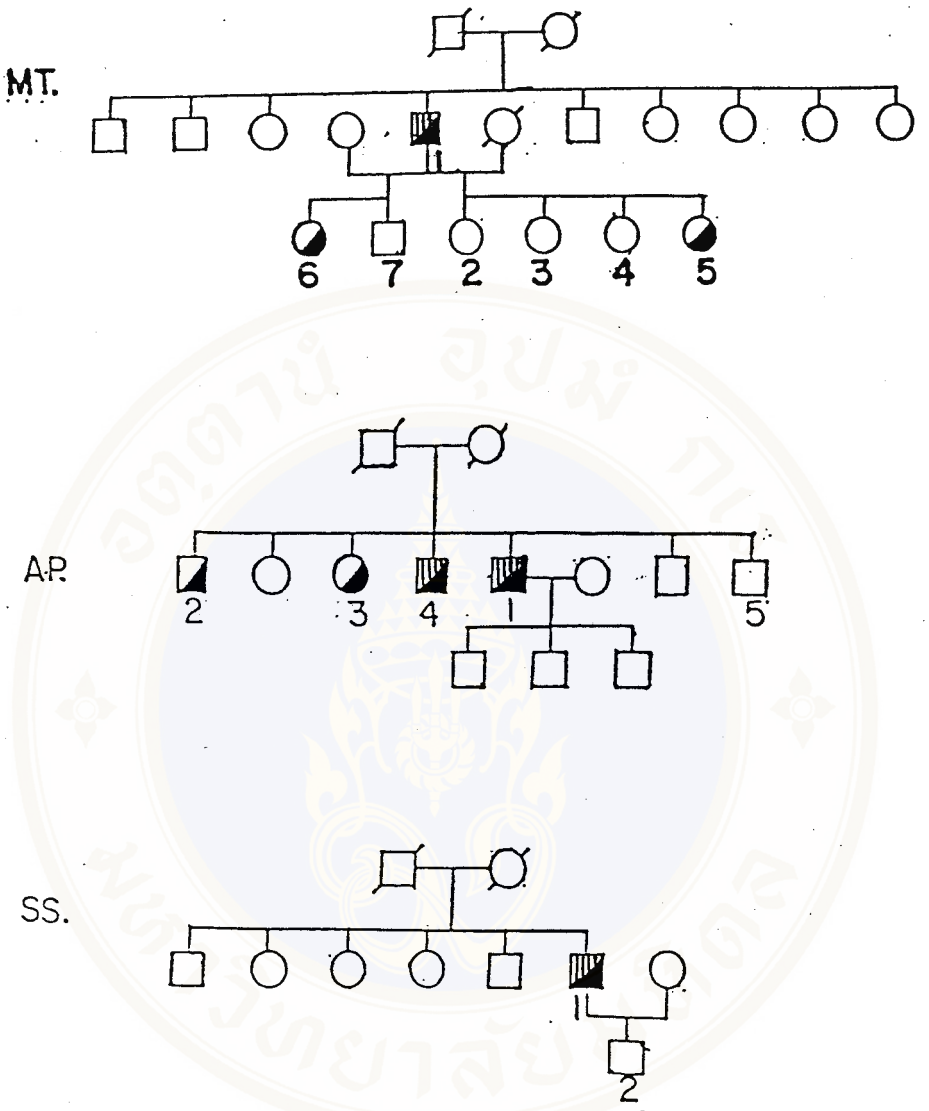

Figure 6. Pedigrees of families MT, AP, and SS. Case numbers are subjects attending Nutrition Clinic and correspond to Table 42. See legends of Figure 2 and 3 for the explanation of symbols.

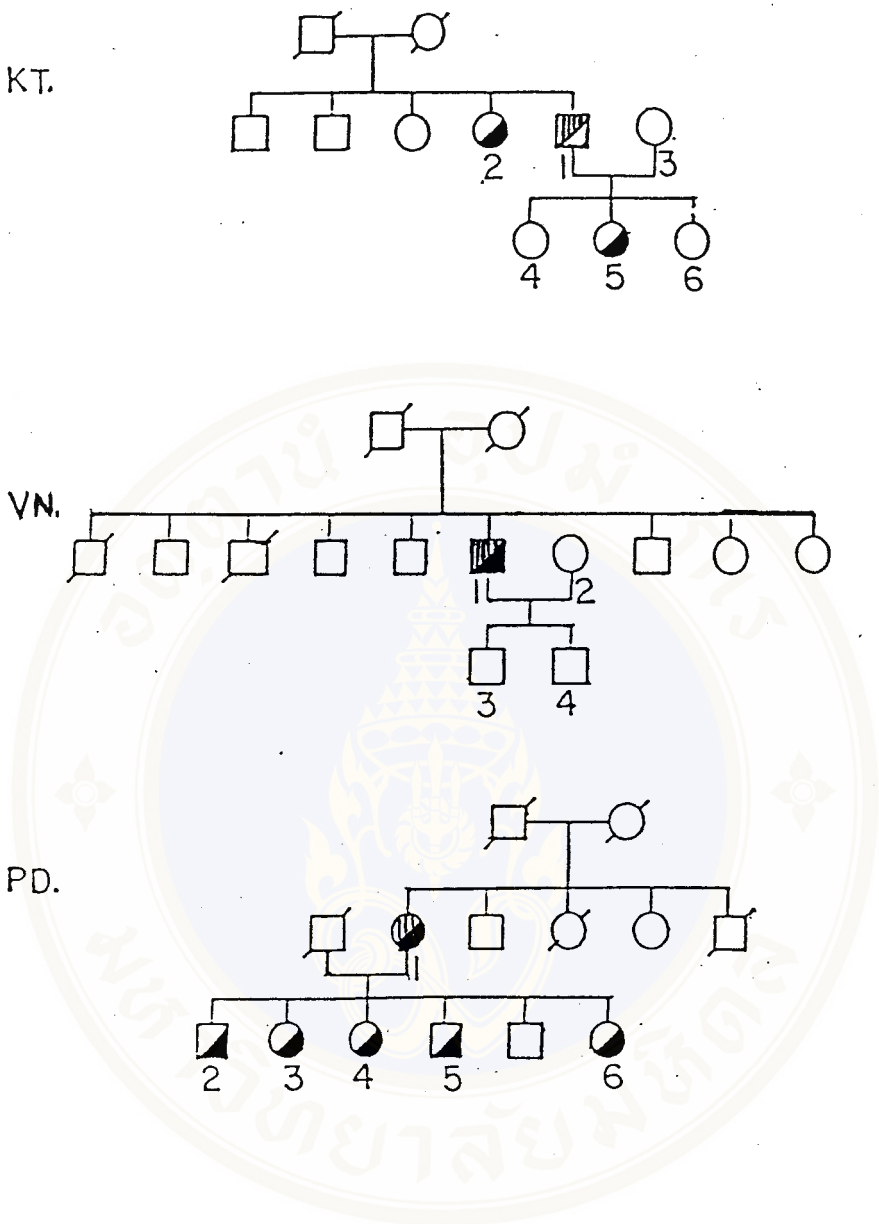

Figure 7. Pedigrees of families KT, VS and PD. Case numbers are subjects attending Nutrition Clinic and correspond to Table 43. See legends of Figure 2 and 3 for the explanation of symbols.

Table 44. Dietary intake in 26 first-line relatives

Subject		Mean±SEM						
Sex	N	Energy	Protein	Fat	Carbohydrate	Protein	Fat	Carbohydrate
		kcal/caput/day	g/caput/day			% of total calories		
Male	9	1699±147	72.0±28.6	71.2±7.9	192.7±18.2	17.1±1.0	37.4±1.9	45.5±2.0
Female	17	1578±78	61.7±6.7	70.1±6.2	175.1±13.0	15.3±1.2	39.1±2.6	45.6±3.5
Total	26	1620±71	65.3±5.0	70.5±4.8	181.2±10.5	15.9±0.9	38.5±1.8	45.6±2.4

energy intake and its distribution.

Anthropometric measurement

Table 45 shows height, body weight, and BMI in 29 male and 36 female first-line relatives. Men were significantly taller and heavier than women but their BMI were not significantly different. **Table 46** shows that out of 65 first-line relatives, 47.7% were underweight and 23.1% were obese.

Waist and hip circumferences were measured in 59 first-line relatives. **Table 47** shows that men had significantly higher waist/hip ratio than women. The prevalences of abdominal obesity in 26 men and 33 women were 1.7 and 13.6%, respectively **(Table 48)**.

Table 49 shows that men had significantly higher UAMC but lower TSF than women. **Table 50** shows that men had significantly lower percentages of body fat than women.

Lipoprotein phenotypes

Out of 65 first-line relatives, 19 were normolipidemic whereas 46 were hyperlipidemic. The later consisted of 38 subjects with type IIa hyperlipoproteinemia, 6 subjects with type IIb hyperlipoproteinemia, and 2 subjects with type IV hyperlipoproteinemia **(Table 51)**. **Table 52** shows serum lipid levels in 65 first-line

Table 45. Height, body weight and BMI in 65 first-line relatives according to sex

Subject		Mean±SEM			
Sex	N	Height	Body weight		BMI
		cm	kg	%std	kg/m^2
Male	29	165.2±1.4 [a1]	57.4±2.2 [a2]	102.2±2.8	21.0±0.7
Female	36	152.0±1.3	50.4±2.0	104.4±3.3	21.7±0.8
Total	65	157.9±1.2	53.5±1.5	103.4±2.2	21.4±0.6

Significant difference from female: [a1] $P<0.0001$, [a2] $P<0.025$

Table 46. Prevalences of underweight, normal weight, and obesity in 65 first-line relatives according to sex

Subject	<20		20.0-24.9		>25.0	
	N	%	N	%	N	%
Male	12	41.4	11	37.9	6	20.7
Female	19	52.8	8	22.2	9	25.0
Total	31	47.7	19	29.2	15	23.1

Table 47. Waist, hip, and waist/hip ratio in 59 first-line relatives according to sex

Subject		Mean±SEM		
Sex	N	Waist	Hip	Waist/Hip ratio
		<-------- cm ------->		
Male	26	72.9±2.1	85.8±1.3	0.85±0.02[al]
Female	33	67.4±2.1	88.6±2.0	0.76±0.01
Total	59	69.8±1.5	87.4±1.3	0.80±0.01

[al] Significant difference from female: P<0.0001

Table 48. Prevalences of abdominal obesity according to sex in 59 first-line relatives

Sex	Total subjects	Prevalence	
		N	%
Male	26	1	1.7
Female	33	8	13.6
Total	59	9	15.3

Table 49. Mid upper arm circumference, upper arm muscle circumference and triceps skinfold thickness in 59 first-line relatives

Subject		Mean±SEM					
Sex	N	UAC		UAMC		TSF	
		cm	%std	cm	%std	cm	%std
Male	26	25.7±0.6	92.1±1.6	21.9±0.5 [a2]	89.8±1.3 [a3]	12.4±0.9 [a1]	113.3±11.8
Female	33	25.1±0.8	92.1±2.6	18.6±0.5	82.4±2.1	20.9±1.3	131.4±7.6
Total	59	25.4±0.5	92.1±1.6	20.0±0.4	85.7±1.4	17.1±1.0	123.4±6.7

Significant difference from female: [a1] P<0.0001, [a2] P<0.0005, [a3] P<0.005

Table 50. Triceps, biceps, subscapular, and suprailiac skinfold thicknesses, and body fat in 59 first-line relatives

Subject		Mean±SEM						
Sex	N	TSF	BS	SS	SI	Sum	Body fat	
		<---------- mm ---------->					%	kg
Male	26	12.4±0.9 [a1]	6.6±0.5 [a1]	18.0±1.7	20.9±2.1	57.4±4.7 [a2]	24.0±1.6 [a1]	14.1±1.6
Female	33	20.9±1.3	12.4±1.0	23.3±2.2	22.6±1.9	79.2±6.2	34.0±1.4	18.1±1.5
Total	59	17.1±1.0	9.8±0.7	21.0±1.5	21.8±1.4	69.6±4.2	29.9±1.3	16.4±1.1

Significant difference from female: [a1] P<0.0001, [a2] P<0.01

Table 51. Lipoprotein phenotypes in 65 first-line relatives and 9 spouses

Lipoprotein phenotype	First-line relatives		Spouses	
	N	%	N	%
IIa	38	58.5	5	55.5
IIb	6	9.2	-	-
IV	2	3.1	-	-
Normal	19	29.2	4	44.4

Table 52. Serum lipid levels in 65 first-line relatives

Serum lipid	Mean±SEM		
	Male (n=29)	Female (n=36)	Total (n=65)
	<---------- mg/dL ---------->		
TC	250.3±17.3	231.8±10.2	240.1±9.6
LDL-C	180.7±16.8	159.4±9.4	168.9±9.1
HDL-C	45.1±1.6	48.7±1.9	47.1±1.3
TG	122.4±11.2	118.8±10.9	120.4±7.8
TC/HDL-C	5.8±0.5	5.0±0.3	5.4±0.3
LDL-C/HDL-C	4.2±0.5	3.5±0.3	3.8±0.3

relatives. Plasma lipoproteins and fibrinogen levels were available in 56 first-line relatives (**Table 53**). **Table 54** shows serum lipid levels in 19 normolipidemic first-line relatives and 38 type IIa, 6 type IIb and 2 type IV hyperlipoproteinemic first-line relatives whereas **Table 55** shows plasma lipoprotein and fibrinogen levels in 56 first-line relatives according to lipoprotein phenotypes.

Fatty acid composition of total serum lipids

Fatty acid composition of total serum lipids was determined in 46 first-line relatives. **Table 56** shows EFA composition of total serum lipids in 46 first-line relatives compared with 83 healthy subjects consisting of 10 men and 73 women which were taken from Tanphaichitr et al., (35). There were no significant differences in serum EFA percentages between male and female first-line realtives. Serum 18:2 n-6, 20:4 n-6, and 20:5 n-3 percentages in first-line relatives were significantly lower than those in healthy subjects whereas the opposite results were observed for serum 20:3 n-6, 18:3 n-3, and 22:6 n-3 percentages. **Table 57** shows that first-line relatives had significantly higher serum 16:0 and 18:0 percentages but significantly lower serum 16:1 n-7 and 18:1 n-9 percentages than healthy subjects.

Table 53. Plasma lipoprotein and fibrinogen levels in 56 first-line relatives

Parameter	Mean±SEM		
	Male (n=24)	Female (n=32)	Total (n=56)
	<---------- mg/dL ---------->		
L-particle	6.5±0.7	7.2±1.6	6.9±0.9
M-particle	52.5±5.5	55.9±4.4	54.5±3.4
S-particle	420.4±26.4	445.2±20.7	434.6±16.3
Fibrinogen	180.8±15.4	194.7±12.6	188.7±9.7

Table 54. Serum lipid levels in 65 first-line relatives according to lipoprotein phenotypes

Serum lipid	Mean±SEM			
	IIa (n=38)	IIb (n=6)	IV (n=2)	Normal (n=19)
	<---------- mg/dL ---------->			
TC	270.2±10.8	305.6±31.3	212,202	162.5±5.2
LDL-C	200.2±10.8	206.8±33.0	128,110	99.5±4.8
HDL-C	47.6±1.7	48.8±5.7	34,41	46.6±1.9
TG	112.2±6.5	248.7±23.3	252,254	82.2±5.7
TC/HDL-C	6.0±0.4	6.6±0.4	6.2,4.9	3.6±0.1
LDL-C/HDL-C	4.5±0.4	4.5±0.8	3.8,2.7	2.2±0.1

Table 55. Plasma lipoprotein and fibrinogen levels in 56 first-line relatives according to lipoprotein phenotypes

Parameter	Mean±SEM			
	IIa (n=31)	IIb (n=5)	IV (n=1)	Normal (n=19)
	<---------- mg/dL ---------->			
L-particle	7.4±1.5	11.4±2.6	17.1	4.5±0.7
M-particle	56.4±4.8	63.5±12.5	22.0	50.7±5.5
S-particle	512.1±22.8	455.2±49.4	392.8	300.2±18.3
Fibrinogen	185.2±14.3	180.1±26.1	149.0	198.8±15.6

Table 56. Mean±SEM of EFA composition of total serum lipids in 46 first-line relatives

Fatty acid	Mean±SEM			
	Healthy (n=83)	Male (n=18)	Female (n=28)	Total (n=46)
	<---------- % total fatty acids ---------->			
18:2 n-6	30.70±0.40	28.33±0.91	28.96±0.94	28.72±0.67 b4
20:3 n-6	1.00±0.08	1.42±0.08	1.37±0.08	1.39±0.06 b2
20:4 n-6	8.10±0.20	6.84±0.33	7.18±0.29	7.05±0.22 b3
18:3 n-3	0.40±0.05	1.43±0.19	1.86±0.11	1.69±0.10 b1
20:5 n-3	0.90±0.10	0.11±0.03	0.16±0.04	0.14±0.03 b1
22:5 n-3	-	0.57±0.14	0.50±0.10	0.52±0.08
22:6 n-3	3.20±0.10	3.76±0.37	4.00±0.29	3.90±0.23 b4
20:3 n-9 / 20:4 n-6	0.02±0.02	0.05±0.01	0.03±0.01	0.04±0.004

Significant difference from healthy: b1 P<0.0001, b2 P<0.0005, b3 P<0.005, b4 P<0.01

Table 57. Mean±SEM of NEFA composition of total serum lipids in 46 first-line relatives

Fatty acid	Mean±SEM			
	Healthy (n=83)	Male (n=18)	Female (n=28)	Total (n=46)
	<---------- % total fatty acids ---------->			
14:0	1.10±0.10	1.16±0.11	1.15±0.11	1.16±0.08
16:0	21.80±0.20	22.72±0.50	22.97±0.63	22.87±0.42 b4
16:1 n-7	2.90±0.10	2.23±0.17	2.58±0.19	2.44±0.13 b3
18:0	6.80±0.10	7.48±0.15	7.60±0.15	7.55±0.11 b1
18:1 n-9	22.00±0.30	19.86±0.63	20.04±0.70	19.97±0.48 b2
20:3 n-9	0.20±0.03	0.32±0.04	0.25±0.04	0.27±0.03

Significant difference from healthy: b1 P<0.0001, b2 P<0.0005, b3 P<0.01, b4 P<0.025

Physical signs and associated conditions

Table 58 shows prevalences of physical signs suggestive of hyperlipidemia in 65 first-line relatives. **Table 59** shows that out of 65 first-line relatives, 15 were obese, 6 were hypertensive, 1 was CHD, 3 were diabetes mellitus, and 6 were smokers.

Effect of dietary advice on lipid status in 18 first-line relatives with hyperlipidemia

As already mentioned, 18 hyperlipidemic first-line relatives attended Nutrition Clinic at Ramathibodi Hospital 8 wk later for the determination of serum lipid levels and fatty acid composition of total serum lipids. They consisted of 5 men and 13 women with mean($\pm$SEM) age 35.3$\pm$4.0 of years and height 155.9$\pm$1.7 of cm.

Anthropometric measurement

Table 60 shows that there were no significant differences in body weight, BMI, UAC, UAMC and TSF between wk 8 and wk 0 of 18 first-line relatives. Similar finding were also observed for their triceps, biceps, subscapular and suprailiac skinfold thicknesses and body fat **(Table 61)**.

Table 58. Number and percentages of 65 first-line relatives with physical signs suggestive of hyperlipidemia according to lipoprotein phenotypes

Lipoprotein phenotype	CA[a]		CA+XA[b]		XA+XL[c]		Total	
	N	%*	N	%*	N	%*	N	%*
IIa	11	16.9	4	6.2	1	1.5	16	24.6
IIb	3	4.6	-	-	-	-	3	4.6
IV	1	1.5	-	-	-	-	1	1.5

[a] [b] [c] Corneal arcus; xanthoma; xanthelasma

* Based on 65 first-line relatives

Table 59. Number and percentages of associated conditions in 65 first-line relatives

Condition	N	% *
Obesity	15	23.1
Hypertension	6	9.2
CHD	1	1.5
Diabetes mellitus	3	4.6
Smoking	6	9.2

* Based on 65 subjects

Table 60. Body weight, BMI, upper arm circumference, upper arm muscle circumference and triceps skinfold thickness in 18 first-line relatives with type IIa hyperlipoproteinemia

Parameter		Mean±SEM	
		Wk 0	Wk 8
Body weight	kg	53.8±2.4	53.5±2.4
	%std	106.5±5.0	105.5±5.1
BMI	kg/m^2	22.4±1.2	22.2±1.3
UAC*	cm	26.6±1.3	26.5±1.3
	%std	93.4±4.4	92.9±4.5
UAMC*	cm	20.5±1.0	20.5±0.9
	%std	85.8±3.8	85.7±3.8
TSF*	mm	19.6±2.2	19.3±1.9
	%std	125.7±12.2	125.0±11.3

* Data were available from 16 patients

Table 61. Triceps, biceps, subscapular and suprailiac skinfold thicknesses and body fat in 16 first-line relatives with type IIa hyperlipoproteinemia

Parameter		Mean±SEM	
		Wk 0	Wk 8
TSF	mm	19.6±2.2	19.3±1.9
BS	mm	12.2±1.5	12.1±1.7
SS	mm	27.3±3.5	25.5±3.5
SI	mm	24.8±2.8	23.8±2.7
SUM	mm	83.9±9.0	80.6±9.2
Body fat	%	32.1±2.4	31.5±2.4
	kg	18.2±2.1	17.9±2.1

Lipid status

Table 62 shows that there were no significant differences in serum lipid except HDL-C, plasma lipoprotein and fibrinogen levels and the ratios of TC/HDL-C and LDL-C/HDL-C in 18 first-line relatives who were type IIa hyperlipoproteinemia. **Table 63** shows that serum 18:2 n-6, 20:4 n-6, and 22:6 n-3 percentages at wk 8 were significantly lower than those at wk 0 whereas opposite result was observed for 20:3 n-9/20:4 n-6 ratio. Serum 20:4 n-6 and 22:6 n-3 percentages in first-line relatives at wk 8 and 20:5 n-3 at wks 0 and 8 were significantly lower than those in healthy subjects whereas opposite results were observed for serum 20:3 n-6 percentage at wk 0, serum 18:3 n-3 percentages at wk 0 and wk 8 (**Table 63**). **Table 64** shows that serum 16:1 n-7 relatives at wk 8 was significantly higher than that at wk 0. Their serum 16:1 n-7 percentage at wk 0, serum 18:0 and 18:1 n-9 percentages at wk 0 and wk 8 were significantly lower than those in healthy subjects whereas opposite result was observed for serum 20:3 n-9 at wk 8.

Table 62. Serum lipid, plasma lipoprotein and fibrinogen levels in 18 first-line relatives with type IIa hyperlipoproteinemia

Parameter		Mean±SEM	
		wk 0	wk 8
TC	mg/dL	259.6±11.4	258.8±14.7
LDL-C	mg/dL	185.7±11.8	192.8±14.3
HDL-C	mg/dL	51.8±2.2	43.6±1.5 [c1]
TG	mg/dL	105.1±9.3	112.3±12.6
TC/HDL-C		5.3±0.5	6.1±0.5 [c2]
LDL-C/HDL-C		3.9±0.5	4.6±0.4 [c2]
L-particle	mg/dL	5.2±0.4	4.4±0.5
M-particle	mg/dL	102.5±11.7	110.0±17.9
S-particle	mg/dL	516.1±22.5	512.6±28.6
Fibrinogen	mg/dL	176.0±21.0	181.4±15.6

Significant difference from wk 0: [c1] $P<0.01$, [c2] $P<0.025$

Table 63. Mean±SEM of EFA composition of total serum lipids in 18 first-line relatives with type IIa hyperlipoproteinemia

EFA	Healthy	First-line relative	
		Wk 0	Wk 8
	<------- % of total fatty acids ----->		
18:2 n-6	30.70±0.40	30.59±1.12	28.27±1.24 c3
20:3 n-6	1.00±0.08	1.35±0.11 b3	1.20±0.09
20:4 n-6	8.10±0.20	7.75±0.32	5.56±0.18 b1,c1
18:3 n-3	0.40±0.05	1.81±0.09 b1	1.74±0.16 b1
20:5 n-3	0.90±0.10	0.12±0.04 b1	0.21±0.02 b1
22:5 n-3	-	0.51±0.12	0.42±0.03
22:6 n-3	3.20±0.10	3.94±0.39	2.60±0.14 b2,c2
20:3 n-9 / 20:4 n-6	0.02±0.02	0.03±0.01	0.06±0.01 c4

Significant difference from healthy: b1 P<0.0001
b2 P<0.005, b3 P<0.025

Significant difference from wk 0: c1 P<0.0001
c2 P<0.005, c3 P<0.025, c4 P<0.05

Table 64. Mean±SEM of NEFA composition of total serum lipids in 18 first-line relatives with type IIa hyperlipoproteinemia

NEFA	Healthy	First-line relative	
		Wk 0	Wk 8
	<------- % of total fatty acids ----->		
14:0	1.10±0.10	1.02±0.10	1.00±0.10
16:0	21.80±0.20	21.78±0.60	22.63±0.47
16:1 n-7	2.90±0.10	2.16±0.26 b3	2.54±0.22 c1
18:0	6.80±0.10	7.53±0.21 b3	7.34±0.17 b4
18:1 n-9	22.00±0.30	18.62±0.67 b1	19.04±0.59 b2
20:3 n-9	0.20±0.03	0.25±0.04	0.31±0.04 b5

Significant difference from healthy: b1 P<0.0001
b2 P<0.0005, b3 P<0.005, b4 P<0.025, b5 P<0.05
Significant difference from wk 0: c1 P<0.01

Effect of drug treatment in 7 first-line relatives with hyperlipidemia

Anthropometric measurement

Table 65 shows that there were no significant changes in body weight, BMI, UAC, UAMC, and TSF during the study in 7 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug. Similar findings were also observed for body fat **(Table 66)**.

Lipid status

Table 67 shows serum lipid, plasma lipoprotein and fibrinogen levels in 7 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug. Their serum HDL-C level at wk 8 was significantly lower than that at wk 0 whereas opposite results were observed for serum TC/HDL-C and LDL-C/HDL-C ratios. Their serum TC, LDL-C, TG, TC/HDL-C, LDL-C/HDL-C as well as plasma S-particle levels at wks 16 and 24 were significantly lower than those at wk 8. Similar findings were also observed between wk 24 and wk 0 for serum TC, LDL-C, TC/HDL-C and LDL-C/HDL-C as well as plasma M- and S-particles levels Their serum HDL-C levels at wks 16 and 24 were significantly higher than that at wk 8. **Table 68** shows that the mean decreases in serum TC, LDL-C, and TG at wk 24 from wk 8 were 21.6, 29.7 and 42.2%, respectively

Table 65. Body weight, BMI, upper arm circumference, upper arm muscle circumference and triceps skinfold thickness in 7 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug

Parameter		Mean±SEM		
		Wk 0	Wk 8	Wk 16
Body weight *	kg	58.5±4.7	58.3±4.7	58.8±5.0
	%std	116.3±9.4	116.1±9.5	116.9±10.1
BMI **	kg/m^2	25.1±2.3	25.0±2.3	25.2±2.4
UAC	cm	28.7±2.5	29.0±2.6	28.9±2.2
	%std	101.6±8.2	102.7±8.4	102.8±7.1
UAMC	cm	21.4±1.9	21.7±1.9	22.0±1.4
	%std	90.1±8.0	91.2±8.0	92.4±6.0
TSF	mm	23.2±2.8	23.4±2.7	22.1±3.4
	%std	149.8±15.7	153.0±16.4	140.7±22.3

* Body weight at wk 24 in 5 subjects was 60.8±5.5 kg and 122.1±11.7 % standard

** BMI at wk 24 in 5 subjects was 26.6±2.9 kg/m^2

Table 66. Triceps, biceps, subscapula and suprailiac skinfold thicknesses and body fat in 7 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug

Parameter		Mean±SEM		
		Wk 0	Wk 8	Wk 16
TSF	mm	23.2±2.8	23.4±2.7	22.1±3.4
BS	mm	14.6±2.6	15.5±2.8	12.4±2.2 cl
SS	mm	32.2±5.6	31.5±5.5	29.1±5.3 cl
SI	mm	29.2±4.3	28.2±4.5	28.8±4.2
SUM	mm	99.2±13.7	98.6±13.8	92.4±13.8
Body fat	%	34.5±3.3	34.3±3.2	34.7±3.9
	kg	20.7±3.3	20.6±3.2	21.1±3.8

cl Significant difference from wk 0: $P<0.025$

Table 67. Serum lipid, plasma lipoprotein and fibrinogen levels in 7 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug

Parameter	Mean±SEM			
	wk 0	wk 8	wk 16	wk 24 (n=5)
TC mg/dL	275.9±15.6	289.0±23.1	242.2±23.9 d5	229.0±28.6 c2,d5
LDL-C mg/dL	196.2±16.0	218.5±23.5	170.0±27.2 d3	155.7±28.6 c4,d3
HDL-C mg/dL	50.7±3.8	40.7±3.2 C3	57.4±5.1 d4	53.3±5.1 d5
TG mg/dL	130.5±12.9	149.1±25.0	80.6±7.8 c3,d5	99.9±18.5 d5
TC/HDL-C	5.7±0.72	7.4±0.9 c1	4.6±0.8 c1,d2	4.6±1.0 c2,d2
LDL-C/HDL-C	4.1±0.6	5.6±0.8 c1	3.3±0.8 c4,d1	3.2±1.0 c3,d2
L-particle mg/dL	6.4±0.7	5.9±1.0	4.1±0.3	4.9±1.6
M-particle mg/dL	142.0±15.5	159.6±35.4	78.0±13.5 c2	83.2±14.9 c4
S-particle mg/dL	543.5±30.4	566.5±45.5	483.8±48.2 d4	447.1±57.1 c3,d5
Fibrinogen mg/dL	208.9±34.7	173.7±24.8	221.2±24.6	242.7±50.5

Significant difference from wk 0: c1 P<0.005, c2 P<0.01, c3 P<0.025, c4 P<0.05

Significant difference from wk 8: d1 P<0.001, d2 P<0.005, d3 P<0.01, d4 P<0.025, d5 P<0.05

Table 68. Net changes of serum lipid levels in 7 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug

Parameter	TC	LDL-C	HDL-C	TG
wk 8 VS wk 0	4.5±5.0	11.1±7.1	-18.7±5.1	10.7±10.8
wk 16 VS wk 0	-12.9±4.8 f2	-15.6±8.2 f1	13.5±6.0 f1	-33.1±11.7
wk 24 VS wk 0	-21.5±4.6 f2	-27.1±7.1 f2	3.0±2.4 f2	-30.9±13.0 f2
wk 16 VS wk 8	-16.0±4.6	-23.7±5.7 f1	45.5±17.2 f1,j1	-34.4±13.0
wk 24 VS wk 8	-21.6±6.9	-29.7±6.7	36.6±12.9 h1,f2	-42.2±9.4 f2
wk 24 VS wk 16	-6.1±7.2	-8.5±10.0 j1	-6.5±8.3 j1	24.6±11.4 g2,h1,i1,j1

*
No of patients = 5

Significant difference from
- wk 8 vs wk 0: f1 P<0.025, f2 P<0.05
- wk 16 vs wk 0: g1 P<0.025, g2 P<0.05
- wk 24 vs wk 0: h1 P<0.05
- wk 16 vs wk 8: i1 P<0.05
- wk 24 vs wk 8: j1 P<0.05

whereas the mean increase in serum HDL-C at the corresponding peroid was 36.6%. **Table 69** shows that serum 20:3 n-6 percentage at wk 16 and 18:3 n-3 percentages at wks 0 and 8 in 5 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug were significantly higher than those in healthy subjects whereas their serum 20:4 n-6 percentages at wks 8 and 16 as well as their serum 20:5 n-3 percentages at wks 0, 8 and 16 were significantly lower than those in healthy subjects. Their serum 20:4 n-6 and 22:6 n-3 percentages at wks 8 and 16 were significantly lower than those at wk 0. Their serum 20:5 n-3 percentage at wk 8 and 20:3 n-9/20:4 n-6 ratios at wks 8 and 16 were significantly higher than those at wk 0. **Table 70** shows that their serum 16:1 n-7 percentage at wk 0 and 18:1 n-9 percentage at wk 8 were significantly lower than those in healthy subjects whereas their serum 18:0 percentage at wk 0 was significantly higher than that in healthy subjects. Their serum 20:3 n-9 percentages at wks 8 and 16 were significantly higher than that at wk 0.

Other laboratory findings

Table 71 shows hematological parameters whereas **Table 72** shows liver and renal function tests, serum enzyme, mineral and carbon dioxide levels in 5 first-line relatives with type IIa hyperlipoproteinemia at wk 0.

Table 69. Mean±SEM of EFA composition of total serum lipids in 5 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug

EFA	Healthy	Subject		
		Wk 0	Wk 8	Wk 16
		<----- % of total fatty acids ------->		
18:2 n-6	30.70±0.40	30.74±1.03	28.22±2.82	25.67±2.97
20:3 n-6	1.00±0.08	1.38±0.19	1.35±0.17	1.76±0.31 b2
20:4 n-6	8.10±0.20	7.03±0.45	5.73±0.25 b1,c2	6.28±0.35 b3,c3
18:3 n-3	0.40±0.05	1.73±0.10 b1	1.41±0.36 b3	1.21±0.51
20:5 n-3	0.90±0.10	0.05±0.05 b1	0.26±0.03 b1,c2	0.22±0.03 b1
22:5 n-3	-	0.32±0.22	0.46±0.08	0.36±0.04
22:6 n-3	3.20±0.10	3.71±0.39	2.82±0.26 c3	2.59±0.32 c1
20:3 n-9 / 20:4 n-6	0.02±0.02	0.01±0.01	0.06±0.01 c2	0.04±0.002 c2

Significant difference from healthy: b1 P<0.0001, b2 P<0.025 b3 P<0.05

Significant difference from wk 0: c1 P<0.0001, c2 P<0.025 c3 P<0.05

Table 70. Mean±SEM of NEFA composition of total serum lipids in 5 first-line relatives with type IIa hyperlipoproteinemia on antihyperlipidemic drug ปริมาณ

NEFA	Healthy	Subject		
		wk 0	wk 8	wk 16
		<----- % of total fatty acids ---->		
14:0	1.10±0.10	1.10±0.22	0.92±0.19	0.86±0.17
16:0	21.80±0.20	22.52±0.47	22.41±0.65	22.47±0.98
16:1 n-7	2.90±0.10	2.03±0.31 b2	2.42±0.49	2.90±0.58
18:0	6.80±0.10	7.66±0.30 b2	7.59±0.29	7.58±0.40
18:1 n-9	22.00±0.30	20.50±0.62	19.20±0.61 b1	21.03±1.54
20:3 n-9	0.20±0.03	0.09±0.06	0.36±0.06 c1	0.27±0.02 c1

Significant difference from healthy: b1 P<0.025, b2 P<0.05

Significant difference from wk 0: c1 P<0.05

Table 71. Hematological parameters in 5 first-line relatives with type IIa hyperlipoproteinemia at week 0

Parameter	Mean±SEM
Hb (g/dL)	14.4±0.4
PVC (%)	42.4±1.0
WBC ($X10^3$ cells/mm^3)	6.1±0.7
Total lymphocyte count ($X10^3$ cells/mm^3)	2.4±0.2
Neutrophil (%)	55.6±3.5
Lymphocyte (%)	39.4±3.3

Table 72. Liver and renal function tests, serum enzyme, mineral and carbon dioxide levels in 5 first-line relatives with type IIa hyperlipoproteinemia at week 0

Parameter	Mean±SEM
Serum total protein (g/L)	70.6±1.3
Serum albumin (g/L)	44.7±1.1
Serum total bilirubin (mg/dL)	1.1±0.2
Serum direct bilirubin (mg/dL)	0.3±0.05
SGOT (U/L)	21.4±3.0
SGPT (U/L)	18.2±5.5
Serum alkaline phosphatase (U/L)	51.4±3.6
CPK (U/L)	88.6±11.6
Serum urea nitrogen (mg/dL)	13.0±1.1
Serum creatinine (mg/dL)	0.9±0.1
Sodium (meq/L)	140.8±0.7
Potassium (meq/L)	4.4±0.2
Chloride (meq/L)	107.2±1.0
CO_2 (meq/L)	25.8±1.3
Calcium (mg/dL)	9.1±0.1
Phosphorus (mg/dL)	3.9±0.3

One yr follow-up in 8 normolipidemic first-line relatives

Table 73 shows that there were no significant differences in body weight and BMI between yr 1 and yr 0 in 8 normolipidemic first-line relatives. **Table 74** shows their serum lipid, plasma lipoprotein and fibrinogen levels. Only plasma M-particle level at yr 1 was significantly lower than that at yr 0.

Study in 9 spouses

Only 1 husband and 8 wives of 9 known hyperlipidemic patients participated in the study. **Table 75** shows their anthropometric parameters. **Table 76** shows their serum lipid, plasma lipoprotein and fibrinogen levels.

Out of 5 hyperlipidemic spouses, 2 received dietary advice for 8 wks and followed by fenofibrate treatment for 16 wks. Their ages were 55 and 59 yr. One was male and the other was female. Their anthropometric parameters are shown in **Tables 77 and 78**. Before receiving fenofibrate, both of them were type IIa hyperlipoproteinemia. **Table 79** shows their serum lipid, plasma lipoprotein and fibrinogen levels. **Tables 80 and 81** show their EFA and NEFA composition of total serum lipids. **Table 82** shows their hematological parameters whereas **Table 83** shows their liver and renal function tests, serum enzyme, mineral, and carbon dioxide levels.

Table 73. Body weight and BMI in 8 normolipidemic first-line relatives

Parameter		Mean±SEM	
		Yr 0	Yr 1
Body weight	kg	41.0±4.1	43.6±3.6
	%std	88.1±3.5	95.6±4.4
BMI	kg/m^2	17.1±0.8	18.4±0.6

Table 74. Serum lipid, plasma lipoprotein and fibrinogen levels in 8 normolipidemic first-line relatives

Parameter		Mean±SEM	
		Yr 0	Yr 1
TC	mg/dL	155.8±7.6	154.8±7.0
LDL-C	mg/dL	92.8±6.5	92.4±5.9
HDL-C	mg/dL	47.0±3.1	47.9±2.0
TG	mg/dL	79.2±4.6	71.6±10.0
TC/HDL-C		3.4±0.2	3.2±0.2
LDL-C/HDL-C		2.0±0.2	1.9±0.1
L-particle	mg/dL	4.6±0.9	4.7±1.2
M-particle	mg/dL	87.6±10.8	45.6±9.4 el
S-particle	mg/dL	300.4±17.5	307.1±13.3
Fibrinogen	mg/dL	189.5±34.2	177.8±65.9

el
Significant difference from yr 0: $P<0.05$

Table 75. Anthropometric parameters in 9 spouses

Parameter		N	Mean±SEM
Height	cm	9	156.2±2.8
Body weight	kg	9	55.0±3.1
	%std	9	108.4±3.8
BMI	kg/m^2	9	22.4±0.7
UAC	cm	8	26.8±0.9
	%std	8	93.6±2.7
UAMC	cm	8	19.9±1.0
	%std	8	84.6±3.1
TSF	mm	8	22.0±1.3
	%std	8	137.4±6.6
BS	mm	8	12.0±1.2
SS	mm	8	26.0±2.3
SI	mm	8	28.5±2.8
Sum	mm	8	88.5±5.9
Body fat	%	8	38.6±1.4
	kg	8	21.4±1.4

Table 76. Serum lipid, plasma lipoprotein and fibrinogen levels in 9 spouses

Parameter		Mean±SEM
TC	mg/dL	234.5±15.4
LDL-C	mg/dL	161.3±13.5
HDL-C	mg/dL	50.4±4.5
TG	mg/dL	114.0±13.6
TC/HDL-C		4.9±1.5
LDL-C/HDL-C		3.4±1.3
L-particle	mg/dL	10.7±4.9
M-particle	mg/dL	62.0±4.9
S-particle	mg/dL	458.1±30.2
Fibrinogen	mg/dL	191.3±23.1

Table 77. Body weight, BMI, upper arm circumference, upper arm muscle circumference and triceps skinfold thickness in 2 sponses with type IIa hyperlipoproteinemia on fenofibrate

Parameter			S.RC				S.PS			
			Wk 0	Wk 8	Wk 16	Wk 24	Wk 0	Wk 8	Wk 16	Wk 24
Body weight		kg	76.2	77.4	77.0	77.2	49.9	49.3	51.0	50.5
		%std	118.3	120.2	119.6	119.9	104.9	103.6	107.2	106.2
BMI		kg/m^2	24.3	24.7	24.6	24.7	22.9	22.6	23.6	23.2
UAC	cm		31.4	-	-	-	25.8	26.7	27.7	-
	%std		107.2	-	-	-	90.5	93.7	97.2	-
UAMC	cm		25.9	-	-	-	19.5	19.3	21.7	-
	%std		102.4	-	-	-	84.1	83.2	93.7	-
TSF	mm		17.5	-	-	-	20.0	23.6	19.0	-
	%std		140.0	-	-	-	121.2	143.0	115.2	-

Table 78. Triceps, biceps, subscapular and suprailiac skinfold thicknesses and body fat in 2 spouses with type IIa hyperlipoproteinemia on fenofibrate

Parameter		S.RC			S.PS		
		Wk 0	Wk 8	Wk 16	Wk 0	Wk 8	Wk 16
TSF	mm	17.5	-	-	20.0	23.6	19.0
BS	mm	8.6	-	-	11.0	14.9	13.0
SS	mm	28.1	-	-	32.9	28.5	28.2
SI	mm	25.1	-	-	27.6	26.9	32.6
SUM	mm	79.3	-	-	91.5	93.9	92.8
Body fat	%	33.6	-	-	41.4	41.7	41.6
	kg	25.6	-	-	20.7	20.6	21.2

Table 79. Serum lipid, plasma lipoprotein and fibrinogen levels in 2 spouses with type IIa hyperlipoproteinemia on fenofibrate

Parameter		S.RC				S.PS			
		Wk 0	Wk 8	Wk 16	Wk 24	Wk 0	Wk 8	Wk 16	Wk 24
TC	mg/dL	263.8	272.5	242.0	219.0	277.0	278.0	249.0	215.0
LDL-C	mg/dL	196.2	201.5	172.0	151.0	186.9	200.4	158.0	124.0
HDL-C	mg/dL	35.0	40.6	53.0	53.0	66.7	53.4	77.0	75.0
TG	mg/dL	163.3	152.4	87.0	74.0	117.1	121.5	70.0	82.0
TC/HDL-C		7.5	6.7	4.6	4.1	4.2	5.2	3.2	2.9
LDL-C/HDL-C		5.6	5.0	3.2	2.8	2.8	3.8	2.0	1.6
L-particle	mg/dL	13.5	27.0	24.3	11.7	3.6	5.4	3.6	3.6
M-particle	mg/dL	199.6	199.6	144.0	76.4	110.0	110.0	76.4	132.4
S-particle	mg/dL	506.1	524.4	471.0	460.0	550.9	553.0	498.0	416.0
Fibrinogen	mg/dL	183.6	261.4	346.0	238.0	129.6	283.0	354.0	229.0

Table 80. EFA composition of total serum lipids in 2 spouses with type IIa hyperlipoproteinemia on fenofibrate

Parameter	S.RC			S.PS		
	Wk 0	Wk 8	Wk 16	Wk 0	Wk 8	Wk 16
	<---------- % of total fatty acids ---------->					
18:2 n-6	27.17	25.26	26.39	24.39	23.72	19.27
20:3 n-6	1.28	1.29	1.41	1.77	1.68	1.90
20:4 n-6	7.66	5.72	5.37	7.71	5.73	4.71
18:3 n-3	1.84	1.81	0.00	2.41	2.20	2.46
20:5 n-3	0.00	0.36	0.23	0.14	0.16	0.10
22:5 n-3	0.00	0.54	0.28	1.66	0.37	0.30
22:6 n-3	4.86	3.17	2.04	4.31	2.56	1.32
20:3 n-9 / 20:4 n-6	0.06	0.05	0.06	0.04	0.07	0.06

Table 81. NEFA composition of total serum lipids in 2 spouses with type IIa hyperlipoproteinemia on fenofibrate

Parameter	S.RC			S.PS		
	Wk 0	Wk 8	Wk 16	Wk 0	Wk 8	Wk 16
	<---------- % of total fatty acids ---------->					
14:0	2.63	1.70	1.04	1.11	1.31	0.89
16:0	24.24	24.84	25.47	19.97	20.88	25.21
16:1 n-7	2.82	2.30	3.02	2.82	3.97	5.00
18:0	6.54	7.57	7.27	8.04	8.33	7.74
18:1 n-9	19.18	20.05	21.63	19.84	18.74	24.85
20:3 n-9	0.50	0.29	0.32	0.30	0.39	0.23

Table 82. Hematological parameters in 2 spouses with type IIa hyperlipoproteinemia

Parameter	S.RC		S.PS
	Wk 0	Wk 8	Wk 0
Hb (g/dL)	13.8	13.4	14.8
PVC (%)	44.9	39.7	43
WBC ($X10^3$ cells/mm^3)	6.2	7.2	6.0
Total lymphocyte count ($X10^3$ cells/mm^3)	3.1	2.7	1.3
Neutrophil (%)	47.0	57.0	78.0
Lymphocyte (%)	50.0	37.0	21.0

Table 83. Liver and renal function tests, serum enzyme, serum mineral and carbon dioxide levels in 2 spouses with type IIa hyperlipoproteinemia at week 0 and 8

Parameter	S.RC		S.PS	
	Wk 0	Wk 8	Wk 0	Wk 8
Serum total protein (g/L)	79.1	76.1	74.9	78.9
Serum albumin (g/L)	50.7	45.2	46.4	45.9
Serum total bilirubin (mg/dL)	0.9	0.8	0.4	0.6
Serum direct bilirubin (mg/dL)	0.3	0.2	0.2	0.2
SGOT (U/L)	17.0	30.0	21.0	63.0
SGPT (U/L)	10.0	31.0	11.0	44.0
Serum alkaline phosphatase (U/L)	52.0	53.0	57.0	48.0
CPK (U/L)	118.0	124.0	69.0	76.0
Serum urea nitrogen (mg/dL)	13.0	12.0	15.0	12.0
Serum creatinine (mg/dL)	1.0	1.2	1.0	1.0
Sodium (meq/L)	142.0	139.0	142.0	145.0
Potassium (meq/L)	4.6	4.6	4.7	4.5
Chloride (meq/L)	104.0	106.0	104.0	113.0
CO_2 (meq/L)	29.0	24.0	28.0	25.0
Calcium (mg/dL)	9.7	9.3	9.5	10.1
Phosphorus (mg/dL)	3.3	3.1	3.3	3.1

DISCUSSION

Identification of causes of hyperlipidemia in known hyperlipidemic patients

Hyperlipidemia is a condition of hypercholesterolemia and/or hypertriglyceridemia.

Hypercholesterolemia (11,93-95)

Hypercholesterolemia are divided into dietary, primary, and secondary hypercholesterolimias.

Dietary hypercholesterolemia is caused by high intakes of saturated fat and cholesterol. Excessive energy intake is also a contributing factor.

Primary hypercholesterolemia is due to hereditary defect in origin and is subdivided into familial hypercholesterolemia,familial combined hyperlipidemia, and polygenic hypercholesterolemia.

Secondary hypercholesterolemia is caused by diseases or conditions affecting LDL metabolism. These include hypothyroidism, obstructive liver desease, nephrotic syndrome, diabetes mellitus, dysproteinemia, and certain drugs, e.g., diuretics and B-adrenergic receptor blockers.

Hypothyroidism tends to be accompanied by hypercholesterolemia, type IIa or IIb, as a consequence of reduced LDL catabolism. Nephrotic syndrome induces elevation of VLDL synthesis as the results of the increase of TG and LDL-C levels. Diuretics induces elevation of LDL-C and VLDL as a consequence of reduced LDL catabolism. An abnormal lipoprotein (Lp-X) is present in serum in the case of intrahepatic and extrahepatic cholestasis. Lp-X is a lipoprotein with motility and has an extremely low percentage of protein, 6% as protein, of which 40% is albumin, but high phospholipid and cholesterol content.

Familial hypercholesterolemia (FH) is a primary genetic defect which produces a decrease in the number of LDL receptors or an alteration in their properties (11,93-95). The disorder is characterized chemically by an elevated plasma concentration of LDL-C; clinically by deposition of cholesterol in specific sites to form xanthomas, corneal arcus and premature coronary heart desease; genetically by autosomal dominant inheritance; and biochemically by a deficiency in the LDL receptor that regulates the degradation of LDL-C. Althongh the FH gene is expressed clinically as an autosomal trait, the disorder is more severe in individuals inheriting two doses of the gene, i.e., homozygotes than in those inheriting one dose, i.e., heterozygotes.

The total plasma cholesterol level in heterozygotes is generally in the range of 270 to 550 mg/dL and rarely exceeds 600 mg/dL. Most untreated adults carrying one FH gene have plasma cholesterol concentrations exceeding 350 mg/dL. In some affected adults, and more often in children, the concentration of total plasma cholesterol is in the range of 250 to 350 mg/dL. The wide variability in cholesterol levels among heterozygotes probably is a reflection of two factors: a. the "normal" allele at the FH locus may exist variant forms among affected individuals and b. the mutant gene exerts its effect within a system of interacting exogenous (environmental) and endogenous (polygenic) factors that are known to modify cholesterol levels. The total plasma cholesterol level in homozygotes is generally in the range of 650 to 1,000 mg/dL. Although some heterozygotes with FH have a slight elevation of the plasma triglyceride concentration, most patients exhibit normal values. The reason for the occasional finding of a plasma triglyceride level of more than 250 mg/dL in some patients with the classic syndrome of familial hypercholesterolemia is not known.

Both homozygotes and heterozygotes may have tendon xanthomas, especially in the Achillis tendons and in the extensor tendons of the hand, tuberous xanthomas, especially over the elbows, and subperiosteal xanthomas, commonly below the knee and over the olecranon process.

Palpebral xanthomas (xanthelasma) are rare in homozygotes, but occur commonly in heterozygotes. Unlike tendon xanthomas, which are virtually diagnostic of FH, xanthelasma can occur in subjects with normal lipid levels and may be transmitted in some families as a genetic trait in the absence of hypercholesterolemia. Elevated orange-yellow planar xanthomas lying superficially in the skin over the extremities, buttocks and hands, especially in the interdigital web between the first and second fingers, are unique to homozygotes and do not occur in heterozygotes. Xanthomas appear in most homozygotes during the first four years of life, but usually do not become manifest in heterozygotes until after age 20. However, many heterozygotes, including most below age 20 and approximately 25 percent of those above age 20 and approximately 25 percent of those above age 20, have only hypercholesterolemia without tendon xanthomas. Corneal arcus appears in about 10% of heterozygotes before 30 years of age and is present in about 50% of heterozygotes above age 30. It usually occurs before age 10 years in homozygotes. Like xanthelasma, corneal arcus can also be observed in patients with normal lipid levels and may appear in several members of the same family.

Fibroblasts cultured from patients with the clinical phenotype of homozygous FH have all displayed evidence of a primary abnormality in the function of the

LDL receptor. Genetic defects can be caused by deletion of part of the coding of LDL receptor gene (96-109). Three different mutations in the gene that specifies the LDL receptor have been identified. One of these mutant alleles, R^{b}, specifies a protein that has no detectable binding activity (< 1% of normal). The second allele, R^{b-}, specifies a protein that has a reduced binding activity (1-10% of normal). The third mutant allele, $R^{b+,io}$, is an extremely rare allele that specifies a protein that can bind LDL normally but that can not catalyze the internalization of the receptor-bound lipoprotein.

Family study in FH reveals that 50 percent of children and one parent of patients are affected. This diagnosis is straightforward if the hypercholesterolemic patient manifests tendon xanthomas or if the patients has a pedigree in which hypercholesterolemia is transmitted vertically in association with tendon xanthomas. The incidence of heterozygous FH is 1:500 whereas that of homozygous FH is 1:1,000,000.

Familial combined hyperlipidemia is a common disorder (11, 93-95) . The LDL receptor activity of these patients was normal. The lipid levels in affected subjects tend to cluster around the 95 the percentile of the general population or only borderline elevation of lipid value, any small change in LDL-C or VLDL level may cause a patient with this disorder to have a normal lipid

level at one time and an abnormal lipid level at another time. Moreover, for similar reasons, the phenotypic expression of the disease may change from time to time (from type IV to type IIb to type IIa and vice versa) as the plasma LDL-C and VLDL levels change only slightly. These patients probably have an increased frequency of obesity, hyperinsulinemia, glucose intolerance and premature coronary heart disease. Tendon xanthomas are not present. In familial combined hyperlipidemia, affected family members have striking variability in the pattern of lipid elevation or they may manifest an elevation of VLDL or LDL or both. Thus, affected individuals in the same family may exhibit any one of three lipoprotein patterns: type IIa, type IIb or type IV.

Polygenic hypercholesterolemia (11, 93-95) By commonly applied criteria, 5 percent of individuals in the general population exhibit LDL-C levels that exceed the 95th percentile and therefore have hypercholesterolemia or combined hyperlipidemia. On the average, among every 20 such hypercholesterolemic persons in whom no secondary cause for the elevated LDL-C level exists, one will have the heterozygous form of FH and three will have familial combined hyperlipidemia. The remaining 16 will have a form of hypercholesterolemia, designated polygenic hypercholesterolemia, that owes its origin not to a single mutant gene of major effect but rather to a complex

interaction of multiple genetic (mildly altered proteins) and environmental factors such as a high cholesterol or high saturated fat diet that affects LDL-C levels in everyone.

Hyperlipidemia is present in no more than 10 per cent of first-line relatives in polygenic hypercholesterolemia by family studies. Patients with polygenic hypercholesterolemia are abcent of tendon xanthoma.

Hypertriglyceridemia (11,93-95)

The characteristic feature of hypertriglyceridemia is an elevation of chylomicron and/or VLDL levels. Hypertriglyceridemia is categorized into dietary, primary, and secondary hypertriglyceridemias.

Dietary hypertriglyceridemia is caused by a high intake of saturated fat and/or carbohydrate, alcohol abuse, and a high caloric intake exceeding energy requirement with lack of physical exercise.

Primary hypertriglyceridemia is inherited disease which is consisted of 5 types, i.e., familial hypertriglyceridemia, familial combined hyperlipidemia, familial lipoprotein lipase deficiency, familial type V hyperlipoproteinemia, and familal type III hyperlipoproteinemia.

Secondary hypertriglyceridemia caused by diseases or conditions affecting chylomicron or VLDL metabolism.

These include diabetes mellitus, alcoholism, pancreatitis, chronic renal failure, dysgammaglobulinemia, glycogen storage disease, and certain drugs, e.g., estrogen.

Familial hypertriglyceridemia is inherited as an autosomal dominant trait. The incidence is estimated to be 2-3 in 1,000 persons. The clinical manifestations are usually not evident until adulthood. This order is often accompanied with obesity, insulin resistance, hyperinsulinemia, glucose intolerance, and hyperuricemia. The xanthoma is absent.

Familial combined hyperlipidemia may manifest as hypercholesterolemia of hypertriglyceridemia as already described.

Familial lipoprotein lipase deficiency is inherited as an autosomal recessive trait. The incidence is estimated to be one in 100,000 persons and this disease is manifested before ago 20. The typical clinical features are eruptive xanthoma, lipemia retinalis, pancreatitis and hepatosplenomegaly. Patients frequently suffer acute attacks of abdominal pain. The serum of this patient displays an extreme increase in chylomicron with normal VLDL level. Serum triglycerides in extreme increased reaching 1,000 to 4,000 mg/dL.

Familial type III hyperlipoproteinemia is an autosomal dominant. The patient has an increase in apo E-2 with concomitant absence of apo E-3 and apo E-4 (apo E-2 homozygosity). The incidence is estimated to be 2-3 in 1,000 persons. The clinical features are planar xanthoma, tuberous xanthoma, and tendon xanthoma. Premature coronary heart disease is often accompanied. The broad beta band is detected by lipoprotein electrophoresis. The serum VLDL-C, TC, and TG are marked elevated.

Familial type V hyperlipoproteinemia is a rare lipid metabolism disorder. The incidence is estimated <1 in 5,000 persons. The elevation of VLDL-TG in addition to chylomicronemia is displayed in this patient. Clinical features are eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, abdominal pain, glucose intolerance, and hyperuricemia. This disease manifests after age 20 yr which is different from familial lipoprotein lipase deficiency.

In our study, 25 known hyperlipidemic patients were able to persuade some of their first-line relatives to attend our Nutrition Clinic. The first-line relatives included parents, siblings, and offsprings of the patients. The total number of first-line relatives from the 25 known hyperlipidemic patients was 235; 179 were alive and 56 were dead. However, only 65 subjects

participated in the study **(Figurel)**. Thus the identification of lipoprotein genotypes in the 25 known hyperlipidemic patients based on the study of their pedigrees was difficult.

Out of 25 known hyperlipidemic patients, 14 were type IIa, 8 were type IIb, and 3 were typeIV hyperlipoproteinemia. It should be noted that the case number 1 shown in **Tables 41-43** and **Figures 2-7** specified the known hyperlipidemic patients. The identification of lipoprotein genotypes for each family was based on serum lipid levels of the known hyperlipidemic patients and their first-line relatives as well as physical signs suggestive of hyperlipidemia as already discussed. Out of 14 known patients with type IIa hyperlipoproteinemia, the diagnosis of FH was conclusive in 9 families including families VS, TS, CP, BY, PV, KK, RC, OR, and SK. In the remaining 5 families including SV, AM, KA, SD, and JB, the cause of hypercholesterolemia was inconclusive because there was lack of complete study of serum lipid levels in the members of the aforesaid families **(Table 41 and Figures 2-4)**.

Out of 8 known patients with type IIb hyperlipoproteinemia, the diagnosis of FH was conclusive in 6 families including families TT, PS, JR, TV, PP, and MT. Family AP was probably familial combined hyperlipidemia because 2 siblings were type IIa, 1 sibling was type IIb, and 1

sibling was type IV hyperlipoproteinemias. The cause of hyperlipidemia in family SS was inconclusive because of lacking complete study of serum lipid levels in the family members **(Table 42 and Figures 5 and 6)**.

Out of 3 known patients with type IV hyperlipoproteinemia, families KT and PD were most likely familial combined hyperlipidemia. The cause of hyperlipidemia in family VN could not be established because the study in siblings of the affected patient was unavailable whereas his 2 sons were 16 and 14 years old who may not have the manifestation of hypertriglyceridemia at this age **(Table 43 and Figure 7)**.

Our study has shown the benefits of the determination of serum lipid levels in the first-line relatives of the affected patients and the examination of physical signs suggestive of hyperlipidemia as the practical mean in identifying hereditary cause of hyperlipidemia. Thus complete pedigree study should be implemented for the firm diagnosis.

Baseline study in 65 first-line relatives

Protein-calorie status

Since dietary intake was assessed only once (wk 0) in 26 first-line relatives and carried out by 24-hr dietary record method the data obtained might represent

the dietary information more on quality than quantity. Though their mean energy intake was 1,620 kcal/day their percentage of fat-calories were 38.5% **(Table 44)** which was higher than the current recommended fat-calorie intake of 30% (1,10).

The mean (±SEM) age of 29 male, 36 female, and 65 total first-line relatives were 31.1±3.1, 33.4±3.0, and 32.4±2.2 years, respectively. Male subjects were significantly taller and heavier than female subjects. However, mean percent standard weight for height and BMI between the 2 sexes were not significantly different **(Table 45)** and were within normal limits (33-34). Besides, their mean waist/hip circumference ratios were also within normal limits **(Table 47)** (110).

The amount of body fat estimated by the sum of the 4 skinfold thicknesses in our female subjects were significantly higher than that in male subjects **(Table 50)** which agrees with the study of Durnin and Wormersley (19). When total values of 40, 60, and 80 mm of the sum of the 4 skinfold thicknesses are considered to be upper normal limit, overweight, and obesity, respectively, these values represents body fat of 19.2, 23.5, and 26.6% of body weight in male subjects and 25.5, 30.6, and 34.4% of body weight in female subjects aged 30-39 years (19). Thus based on the sum of 4 skinfold and body fat content our male subjects were overweight whereas female subjects were

obese **(Table 50)**. The data agree with the prevalences of obesity based on the criteria of BMI, i.e., 20.7% in male subjects and 25.0% in female subjects **(Table 46)**. Besides, the prevalence of abdominal obesity in female subjects was higher than that in male subjects **(Table 48)**. On the other hand, male subjects had better somatic protein status than female subjects evidenced by significantly higher UAMC in the former group than the latter group **(Table 49)**. The result agrees with the existing knowledge (19).

Prevalence of hyperlipidemia

Cholesterol levels are known to be the best predictors for the development of early CHD. Besides, familial patterns of CHD may simply reflect familial patterns in major risk factors, including cholesterol (111). In 1973, Nikkila and Aro (112) studied 412 first-line relatives of 101 young survivors of myocardial infarction and found that their mean serum TC and TG levels were significantly higher than in a control population. The study also showed that type IIa hyper-lipoproteinemia occured 1.8 times, type IV hyperlipopro-teinemia 1.3 times, and type IIb hyperlipoproteinemia 2.5 times more commonly in relatives than in control. In 1980, Hennekens et al., (111) studied 91 offspring of parents with premature myocardial infarction prior to age 50, and reported that these offspring had higher plasma

TC levels than those in 86 control children. In 1983, Morrison et al., (113) studied 841 offspring and 1,236 siblings of normocholesterolemic probands, 833 offspring and 1,194 siblings of hypercholesterolemic probands, and 877 offspring and 1,108 siblings of hypertriglyceridemic probands in the Lipid Research Clinics Collaborative Family Study Program. The probands had three visits. As the categorization of probands' hypercholesterolemia or hypertriglyceridemia increased from sporadic (having only one result ≥90th percentile cholesterol cut point or ≥95 the percentile TG cut point) to persistent (having two or three results ≥90th percentile cholesterl cut point or ≥95th percentile TG cut point), to severe (having two or three results ≥99th percentile cholesterol and TG cut point), the percentage of hypercholesterolemic or hypertriglyceridemic offspring and siblings increased. Their study have shown that close sibling and parent-offspring lipid and lipoprotein risk factor associations in hypercholesterolemic and hypercholesterolemic family units during and after the period of shared common-household environment facilitate within family identification of dyslipoproteinemia and suggest potential sharing of CHD risk.

In our study, 70.8% of 65 first-time relatives of known hyperlipidemic patients were hyperlipidemic consisting of 58.5% as type IIa, 9.2% as type IIb, and

3.1% as type IV hyperlipoproteinemias **(Table 51)**. The mean serum lipid levels in 65 first-line relatives according to the aforesaid 3 lipoprotein phenotypes are shown in **(Table 54)**. It can be visualized that hypercholesterolemia is the major problem of their hyperlipidemia. The prevalence of hypercholesterolemia in this first-line relatives was 67.7% whereas that of 3,494 urban Thais, aged 35-54 years was 69.7% (8).

The mean(±SEM) serum TC, LDL-C, HDL-C, and TG in 29 male first-line relatives were 250.3±17.3, 180.7±16.8, 45.1±1.6, and 122.4±11.2 mg/dL, respectively, whereas the corresponding figures in 2703 urban men were 224.1±0.81, 146.1±0.8, 45.5±0.2, and 165.8±2.4 mg/dL. These serum lipid levels were 231.8±10.2, 159.4±9.4, 48.7±1.9, and 118.8±10.9 mg/dL in 36 female first-line relatives and 219.2±1.5, 145.1±1.4, 52.3±0.4, and 107.9±2.0 mg/dL in 791 urban women **(Table 52)** ( ). Thus these first-line relatives had hypercholesterolemia due to high LDL-C as a risk factor for CHD. It should be noted that 14% of 65 first-line relatives had serum HDL-C of 35 mg/dL and below **(Tables 41-43)**. This explained their high serum TC/HDL-C and LDL-C/HDL-C ratio **(Table 52)**.

EFA status

Tanphaichitr (114) have shown that human inadequate linoleate status can be sequentially categorized into 3 stages biochemical linoleate depletion, biochemical

linoleate deficiency and clinical linoleate deficiency. The diagnosis of biochemical linoleate depletion is based on the decrease in serum linoleate (18:2 n-6) and arachidonate (20:4 n-6) percentages whereas biochemical linoleate deficiency in characterized by the increase in 5, 8, 11-eicosatrienoate/arachidonate (triene/tetraene; 20:3 n-9/20:4 n-6) ratio in addition to the aforementioned biochemical findings. Deleterious effects of human linoleate deficiency include scaly dermatitis, impaired growth, fatty liver, delayed wound healing and low platelet count.

Tanphaichitr et al., (35) have shown that mean (±SEM) 18:2 n-6, 20:4 n-6, and 20:3 n-9/20:4 n-6 ratio measured in 83 normal Thai adults were 30.70±0.40, 8.10±0.20 and 0.02±0.02% of total fatty acids, respectively. Although several studies still use the trienel tetraene ratio of 0.4 as the criteria for the diagerosis of linoleate deficiency, the value of should be used as the upper limit of normality for this ratio (114-116).

Tanphaichitr et al., (117) reported that 10 patients with protein-calorie malnutrition had mean(±SEM) serum linoleate, arachidonate, and oleate (18:1 n-9) levels of 23.7±2.9, 7.9±1.6, and 30.4±2.0%, respectively. After receiving total parenteral nutrition for 7 days, the aforesaid serum fatty acid levels became 8.6±2.6, 3.2±0.4,

and 39.0±2.3%. In another 10 patients with protein-calorie malnutrition who received daily supply of linoleate 8.5% of total energy for 7 days, their serum linoleate, arachidonate, and oleate levels were 38.9±1.1, 4.7±0.6, and 20.1±0.7%, respectively. In our study, EFA status was assessed only in 46 first-line relatives. Their mean(±SEM) serum linoleate and arachidonate levels were 28.7±0.7 and 7.0±0.2%, respectively **(Table 56)** which were higher than patients with protein-calorie malnutrition and patients on fat-free total parenteral nutrition. Opposite results were observed for serum oleate levels **(Table 57)**. Thus the data did not indicate inadequate linoleate status in first-line relative. However, mean serum linoleate and arachidonate levels in first-line relatives were slightly but significantly lower than those in 83 healthy subjects **(Table 56)** whereas opposite results were observed for serum oleate levels **(Table 57)**. This, may reflect lower linoleate intake in first-line relatives than in healthy subjects, could be due to lower arachidonate intake in the former group than the latter group and/or the reduced biotransformation of arachidonate from linoleate. The latter mechanism was supported by the significantly higher serum 20:3 n-6 level in first-line relatives than healthy subjects **(Table 56)**. It should be noted that the mean serum (±SEM) TC and TG in 83 healty subjects were 189.4±8.8 and 125.4±12.8 mg/dL, respectively.

Linoleic acid is the principal PUFA in vegetable seed oils and more prevalent in the diet than 18:3 n-3. However, foods of marine origin are rich sources of 20:5 n-3 and 22:6 n-3, whereas meat, liver, and brain provide 20:4 n-6 (114). The significantly higher serum 18:3 n-3 and 22:6 n-3 levels but lower serum 20:5 n-3 levels in 46 first-line relatives than 83 healthy adults could be due to different sources of intakes of n-3 fatty acids.

Physical signs and associated conditions

Corneal arcus, xanthoma, and xanthelasma detected in 30.7% of 65 first-line relatives **(Table 58)** suggest the cause of their hyperlipidemia was primary in origin and are consistent with the study on this pedigrees already discussed.

Inaddition to hypercholesterolemia, other CHD risk factors induding obesity, hypertension, smoking, and diabetes mellitus were also present in the first-line relatives **(Table 59)**.

Effect of dietary advice on lipid status in hyperlipidemic first-line relatives

As already mentioned in Chapter III, low intakes of saturated fat and cholesterol with high intake of poluunsaturated fat can lower increased serum TC levels. The minimal goals of dietary therapy are to lower serum

LDL-C to levels below the cut points for initiating therapy, i.e., to below 160 mg/dL, or to below 130 mg/dL if definite CHD or two other CHD risk factors are present. Serum TC levels of 240 and 200 mg/dL correspond roughly to LDL-C levels of 160 and 130 mg/dL, respectively. Thus, the monitoring goals during dietary therapy are to lower the serum TC level to below 240 mg/dL with an LDL-C goal of <160 mg/dL, or to below 200 mg/dL with an LDL-C goal of <130 mg/dL (10). The dietary therapy and counseling should be implemented before initiating drug therapy.

In our study, during the first visit, all of the first-line relatives subjects received brochure instructing them to reduce total fat intake to 30% or less of total dietary energy, to increase linoleate intake to 10% of total dietary energy, and to reduce dietary cholesterol to less than 300 mg/day, and they were adviced to have regular exercise and to promote weight loss in subjects who were overweight.

Only 18 hyperlipidemic first-line relatives revisited our Nutrition Clinic 8 weeks later. During the 8-week period there were no significant changes in various anthropometric parameters **(Tables 60 and 61)**. These indicate that they maintained their initial protein-calorie status. Regarding to their serum lipid levels, only serum HDL-C at week 8 was significantly lower than at week 0 **(Table 62)**. Since there was no increase in their

serum linoleate level at week 8 **(Table 63)** this indicates that they did not increase their linoleate intake. This explains why there were no significant decreases in their serum TC and LDL-C levels at week 8 **(Table 62)**. The significantly lower serum arachidonate and docosahexaenoate levels at week 8 than at week 0 were most likely due to the decreased consumption of the direct sources of these 2 essential fatty acids. There were no significant differences in serum 18:1 n-9 and 20:3 n-9 levels between week 8 and week 0 **(Table 64)**. Thus the increase in serum 20:3 n-9/20:4 n-6 ratio at week 8 was due to the decrease in serum 20:4 n-6 level **(Table 23)**. However, the ratio was still lower than 0.2 which indicates the adequacy of their linoleate status.

Though 2 out of 18 hyperlipidemic first-line relatives became normolipidemic the overall results indicate that dietary advice through brochure was unsuccessful.

Effect of drug treatment in 7 first-line relatives with hyperlipidemia

Drug therapy should be considered for patients who do not or can not meet the goals on dietary therapy, have atherosclerotic lesion or other CHD risk factors (10,94-95). The goals of drug therapy are the same as those of dietary therapy: to lower LDL-C to below 160 mg/dL, or to

below 130 mg/dL if definite CHD or two other risk factors are present (10). Drug therapy should be added to dietary therapy, and not substituted for it. In general, maximal efforts should be made in this group to achieve lower cholesterol levels and lower CHD risk by means of non-pharmacologic approaches. Many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-C goal (<130 mg/dL) has not been reached.

In U.S.A., the drugs of first choice are the bile acid sequestrants (cholestyramine, colestipol) and nicotinic acid. Both cholestyramine and nicotinic acid have been shown to lower CHD risk in clinical trials, and their long-term safety has been established. A new class of drugs, to be considered after the bile acid sequestrants and nicotinic acid, is the 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors. These drugs are very effective in lowering LDL-C levels. Other available drugs include fibric acid derivatives (gemfibrozil, bezafibrate, fenofibrate) and probucol. Fibric acid derivatives are primarily effective for lowering elevated TG levels (10,118).

In our study, all of 7 hyperlipidemic first-line relatives were type IIa hyperlipoproteinemia and were treated with fibric acid derivatives starting from week 9: 2 on bezafibrate, 2 on gemfibrozil, and 3 on fenofibrate. The pharmacologic actions of bezafibrate and gemfibrozil

have been already presented in chapter III. For fenofibrate, it has a marked effect in lowering serum TG level by several mechanism, i.e., inhibiting de novo hepatic fatty acid synthesis and hepatic VLDL synthesis by enhancing mitochondrial and peroxysomal fatty acid oxidation and lipoprotein lipase activity. It has also been shown to have cholesterol-lowering activity by inhibiting cholesterol synthesis prior to mevalonate formation, indirectly causing significant reduction of hydroxy methyl glutaryl coenzyme A reductase activity, and possibly inhibiting acyl-coenzyme A-cholesterol transferase activity (119-121).

The reason why these 7 hyperlipidemic first-line relatives received different types of hyperlipidemic drugs because the physicians prescribed the same drugs given to the known hyperlipidemic patients in their family.

The significant decrease in serum TC, LDL-C, TG, M- and S- particles levels as well as significant increase in serum HDL-C level in 7 first-line relatives with type IIa hyperlipoproteinemia are consistent with the effects of the action of fibric acid derivatives **(Tables 67 and 68)**. This was supported by the findings that there were no significant changes in their protein-calorie status **(Tables 65 and 66)** and their serum linoleate levels **(Table 69)**. The changes in their serum 20:4 n-6, 20:5 n-3, and 22:6 n-3 levels were most likely due to the alteration of

dietary sources of these essential fatty acids. However, throughout the study their linoleate status was adequate evidenced by normal 20:3 n-9/20:4 n-6 ratio **(Tables 69 and 70)**. It should also be noted that hematological and other biochemical parameters available in 5 first-line relatives were within normal limits **(Tables 71 and 72)** (122).

One-year follow-up in 8 normolipidemic first-line realtives.

National Cholesterol Education Program (NCEP) has suggested that patients with desirable blood cholesterol levels (<200 mg/dL) should be given general dietary and risk reduction educational materials, and advised to have another serum cholesterol test within five years (10). In our study, 8 out of 19 normolipidemic first-line relatives revisited our Nutrition Clinic 1 yr later. All of them were still normolipidemic. Except, plasma M-particle level there were no significant differences in serum lipid, plasma lipoprotein and fibrinogen levels as well as body weight and BMI between yr 1 and yr 0 **(Tables 73 and 74)**.

Study in 9 spouses

Out of 18 spouses, 9 participated in the study as described in the first-line relatives. Four were normolipidemic and 5 were type IIa hyperlipoproteinemia

(Tables 41-43). Their mean (±SEM) serum lipid, plasma lipoprotein and fibrinogen levels are shown in **Table 76.**

The mean (±SEM) age of 9 spouses was 49.0±2.9 yr **(Table 40)**. Though their mean percent standard weight for height, BMI and UAC were within normal limits (15,33-34) their mean sum 4 skinfold thicknesses and TSF exceeded the upper normal limits whereas their UAMC was below the lower normal limit (15). The data indicate that they were obese with inadequate somatic protein status.

Only 2 spouses with type IIa hyperlipoproteinemia were further managed by dietary advice and fenofibrate. Their initial hematological and other biochemical parameters were within normal limits **(Tables 82 and 83)**. The effects of fenofibrate on lowering serum TC, LDL-C, TG, M- and S-particle levels and increasing serum HDL-C level were also seen in these 2 spouses **(Table 79)** whereas there were no striking changes in their anthropometric parameters **(Tables 77 and 73)** and serum fatty acid levels **(Tables 80 and 81)**.

CHAPTER V

SUMMARY

Since hyperlipidemia is prevalent in urban Thais, it is interested to investigate the cause of their hyperlipidemia. The objectives of our study are to identify the causes of hyperlipoproteinemia in the known hyperlipidemic patients, to assess the effect of treatment on serum lipid levels of the known hyperlipidemic patients and the other risk factors for CHD, and to investigate the prevalence and management of hyperlipidemia in the first-line relatives of the known hyperlipidemic patients.

Invitation and questionnaires were sent to 98 hyperlipidemic patients who attended Nutrition Clinic at Ramathibodi Hospital. Eighty-nine hyperlipidemic patients responded the questionnaires but only 25 hyperlipidemic patients were able to persuade 65 first-line relatives to participate in the study.

The study are presented in 2 parts: study in known hyperlipidemic patients and study in first-line relatives and spouses. The data are shown in mean±SEM.

Study in known hyperlipidemic patients

The study in 89 known hyperlipidemic patients consisting of 30 males and 59 females, aged 51.0±1.2 yr at the initial study can be summarized as follow

1. Anthropometric assessment in 89 hyperlipidemic patients revealed that the prevalences of obesity based on BMI $\geq$25.0 kg/m^2 were 41.6% at the first visit and 42.7% at the inital study. Based on the sum of the four skinfolds and body fat content, male patients were overweight (68.6$\pm$5.3 mm; 27.8$\pm$1.3%) whereas female patients were obese (95.0$\pm$4.0 mm; 39.8$\pm$0.7%). The prevalence of abdominal obesity at the initial study in 28 males was 7.1% and that in 51 females was 49.0%.

2. The following lipoprotein phenotypes were identified at the first visit: 61.8% as type IIa, 30.3% as type IIb, 1.1% as type III, 4.5% as type IV, and 2.2% as type V hyperlipoproteinemias. Corneal arcus, xanthoma, and/or xanthelasma were detected 58% of the patients.

3. In 29 patients with type IIa hyperlipoproteinemia receiving only dietary treatment for 34.8$\pm$41.3 weeks, the net decreases in serum TC and LDL-C levels at the initial study from the first visit were 9.7$\pm$2.1 and 14.1$\pm$3.1%, respectively.

In 8 patients with type IIb hyperlipoproteinemia received only dietary treatment for 83.2$\pm$27.8 weeks there was significant decrease in serum TG only with a mean decrease of 14.0$\pm$5.4%.

4. In 10 patients with type II hyperlipoproteinemia receiving 200-600 mg of bezafibrate treatment daily for 40.3$\pm$18.1 weeks, the mean ($\pm$SEM) decreases serum TC, LDL-

C, and TG levels. were 14.7±4.4, 18.8±5.3 and 31.8±8.7%, respectively. Besides, their serum HDL-C level increased to 29.9±8.8% of the initial level.

In 10 patients with type II hyperlipoproteinemia receiving 600-1,200 mg of gemfibrozil treatment daily for 21.9±6.5 weeks, the mean (±SEM) decrease in serum TG was 50.0±4.1%.

In 13 patients with type II hyperlipoproteinemia receiving 250-1,000 mg of probucol treatment daily for 77.4±31.3 weeks, the mean(±SEM) decreases in serum TC, LDL-C, HDL-C, and TG were -13.3±3.8, -12.9±5.2, -6.3±8.5, and -5.1±25.1%, respectively. The mean(±SEM) decreases in serum TC, LDL-C, and TG after receiving the treatment for 50.2±16.7 weeks were 14.0±3.0, 14.1±3.9 and 5.8±13.6%, respectively for type IIa hyperlipoproteinemic patients and for 32.8±9.9 weeks were 17.0±2.9, 14.0±4.5 and 40.3±5.2%, respectively for type IIb hyperlipoproteinemic patients. The mean(±SEM) increase in serum HDL-C level in the latter group was 8.6±7.1%.

5. None of the 89 hyperlipidemic patients was diabetes mellitus. Male patients had significantly higher hemoglobin and serum uric acid levels than female patients. The prevalences of hyperuricemia, obesity, hypertension, anemia, CHD, smoking, and alcohol drinking in these patients were 68.6, 42.7, 25.8, 16.0, 11.2, 3.4, and 2.2%, respectively.

Study in first-line relatives and spouses

1. Out of 25 known hyperlipidemic patients, 14 were type IIa, 8 were type IIb, and 3 were type IV hyperlipoproteinemia. Out of 14 known patients with type IIa hyperlipoproteinemia, the diagnosis of FH was conclusive in 9 families including families VS, TS, CP, BY, PV, KK, RC, OR, and SK. In the remaining 5 families including SV, AM, KA, SD, and JB, the cause of hypercholesterolemia was inconclusive.

Out of 8 known patients with type IIb hyperlipoproteinemia, the diagnosis of FH was conclusive in 6 families including families TT, PS, JR, TV, PP, and MT. Family AP was probably familial combined hyperlipidemia. The cause of hyperlipidemia in family SS was inconclusive.

Out of 3 known patients with type IV hyperlipoproteinemia, families KT and PD were most likely familial combined hyperlipidemia. The cause of hyperlipidemia in family VN could not be established.

Our study has shown the benefits of the determination of serum lipid levels in the first-line relatives of the affected patients and the examination of physical signs suggestive of hyperlipidemia as the practical mean in identifying hereditary cause of hyperlipidemia. Thus complete pedigree study should be implemented for the firm diagnosis.

2. The mean (±SEM) age of 29 male, 36 female, and 65

total first-line relatives were 31.1±3.1, 33.4±3.0, and 32.4±2.2 years, respectively. Male subjects were significantly taller and heavier than female subjects. However, mean percent standard weight for height and BMI between the 2 sexes were not significantly different and were within normal limits. Besides, their mean waist/hip circumference ratios were also within normal limits.

Thus based on the sum of 4 skinfold and body fat content our male subjects were overweight whereas female subjects were obese. The data agree with the prevalences of obesity based on the criteria of BMI, i.e., 20.7% in male subjects and 25.0% in female subjects. Besides, the prevalence of abdominal obesity in female subjects was higher than that in male subjects. On the other hand, male subjects had better somatic protein status than female subjects.

3. Out of 65 first-line relatives, 46 were hyperlipidemic consisting of 58.5% as type IIa, 9.2% as type IIb, and 3.1% as type IV hyperlipoproteinemias.

4. The mean(±SEM) serum linoleate and arachidonate levels in 46 first-line relatives were 28.7±0.7 and 7.0±0.2%. The mean serum linoleate and arachidonate levels in first-line relatives were slightly but significantly lower than those in 83 healthy subjects. This may reflect lower linoleate intake in first-line

relatives than in healthy subjects whereas low serum arachidonate level could be due to lower arachidonate intake in the former group than the latter group and/or the reduced biotransformation of arachidonate from linoleate.

The significantly higher serum 18:3 n-3 and 22:6 n-3 levels but lower serum 20:5 n-3 levels in 46 first-line relatives than 83 healthy adults could be due to different sources of intakes of n-3 fatty acids.

5. Corneal arcus, xanthoma, and xanthelasma were detected in 30.7% of 65 first-line relatives.

In addition to hypercholesterolemia, other CHD risk factors induding obesity (23.1%), hypertension (9.2%), smoking (9.2%), and diabetes mellitus (4.6%) were also present in the first-line relatives.

6. After receiving brodurre, only 18 hyperlipidemic first-line relatives revisited our Nutrition Clinic 8 weeks later. Only serum HDL-C level at week 8 was significantly lower than that at week 0. Since there was no increase in their serum linoleate arachidonate docosahexaenoate levels at week 8 this indicates that they did not increase their EFA intake.

The overall results indicate that dietary advice through brochure was unsuccessful.

7. All of 7 hyperlipidemic first-line relatives were type IIa hyperlipoproteinemia and were treated with fibric

acid derivatives starting from week 9: 2 on bezafibrate, 2 on gemfibrozil, and 3 on fenofibrate. The significant decrease in serum TC, LDL-C, TG, M-and S- particles levels as well as significant increase in serum HDL-C level in 7 first-line relatives with type IIa hyperlipoproteinemia are consistent with the effects of the action of fibric acid derivatives. The changes in their serum 20:4 n-6, 20:5 n-3, and 22:6 n-3 levels were most likely due to the alteration of dietary sources of these essential fatty acids. However, throughout the study their linoleate status was adequate evidenced by normal 20:3 n-9/20:4 n-6 ratio.

8. Eight out of 19 normolipidemic first-line relatives revisited our Nutrition Clinic 1 yr later. All of them were still normolipidemic.

9. Out of 18 spouses, 9 participated in the study. Four were normolipidemic and 5 were type IIa hyperlipoproteinemia. Their mean percent standard weight for height, BMI and UAC were within normal and limits their mean sum 4 skinfold thicknesses and TSF exceeded the upper normal limits whereas their UAMC was below the lower normal limit.

Only 2 spouses with type IIa hyperlipoproteinemia were further managed by dietary advice and fenofibrate. Their initial hematological and other biochemical parameters were within normal limits. The effects of

fenofibrate on lowering serum TC, LDL-C, TG, M- and S-particle levels and increasing serum HDL-C level were also seen.

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