วารสารเทคนิคการแพทย์ เชียงใหม่
BULLETIN OF CHIANG MAI MEDICAL TECHNOLOGY

Vol. 6 No. 2
May 1973

THE SERUM LIPIDS

I. BIOCHEMISTRY, CLASSIFICATION AND CLINICAL SYNDROMES

Muni Keoplung, M.D. *
Jit Jiraratsatit, M.D. *
Nuntaya Waiwatana, B. Sc. (Med. Tech.) **

The serum lipids are current subjects of great interest, especially, in the etiologies and courses varieties of diseases. Therefore, it is whorthwhile to review their biochemical and clinical view-points before applying them for clinical purposes.

According to Bloor, (I) the classification of the lipids which is generally accepted in the United States and with a few modifications, is as follows :

A. Simple lipids - esters of fatty acids with various alcohols.

1. Neutral fats and oils-triglycerides: triesters of fatty acides with glycerol.
2. Waxes : esters of fatty acids
   a. True waxes
   b. Cholesterol ester : esters of fatty acids with cholesterol
   c. Vitamin A ester : palmitic or stearic acid ester of vitamin A
   d. Vitamin D esters

B. Compound lipids - esters of fatty acids with alcohol plus other groups.

1. Phospholipids : lipids containing phosphoric acid and, in most cases, a nitrogenous base
2. Glycolipids or cerebrocides; lipids containing carbohydrate and also nitrogen but no glycerol
3. Sulfolipids : lipids characterized by possessing sulfate group
4. Lipoproteins : lipids attached to plasma or other proteins
5. Lipopolysaccharides : lipids attached to polysaccharides

C. Derived lipids : derivatives obtained by hydrolysis of those given in group A and B

1. Saturated and unsaturated fatty acids
2. Monoglycerides and diglycerides
3. Alcohols

* Departmen of Medicine, Faculty of Medicine, Chiang Mai University.
** School of Medical Technology, Chiang Mai University.

D. Miscellaneous lipids

1. Aliphatic hydrocarbons
2. Carotenoids
3. Squalene
4. Vitamin A and B

The purpose of this paper is directed to certain lipids that are commonly found or involved in the diseases.

TRIGLYCERIDES : There are triesters of trihydric alcohol glycerol and various fatty acids. They are the most abandant natural lipids. The biosynthesis of triglycerides in the body appearently occurs primary in the liver. It is stored in the adipose tissue. The epithelial cells of the intestinal mucosa are active in this respect.

Triglycerides do not function only as a source of energy : but also solvent for fat - soluble vitamins, aiding in the transport and function of these substances.

PHOSPHOLIPIDS : The phospholipids, mostly produced by the liver, present in all cells and are the second most naturally occurring lipids. Most of them are composed of fatty acids, a nitrogenous base, phosphoric acid, glycerol, inositol and sphingosine. They play vital roles as constituents of cell membrances and factors in regulating membrane permeability. They are present in the myelin sheath of nerve cells and in electron - transport particles.

LIPOPROTEINS : The lipoproteins are extremely important type of lipids because of their vital roles in the solubilization and transport of water - insoluble lipids in the plasma and other aqueous fluids in the body. They are association complex of varying proportions of triglyceride, phospholipid and cholesterol. The protein moieties are primarily formed in the liver (4) and to some extent in the intestinal mucosal cells. The lipid component decreases the density of the lipoproteins. The differences in the content of lipids and proteins among several lipoproteins result in difference densities and permit their further separation by ultracentrifugation. The lipoproteins also differ in their electrical charge. This property, in combination with differencs in size, also permits separation of the lipoproteins into specific bands by electrophoresis.

By their electrophoresis or ultracentrifugation, the plasma lipoproteins are usually considered as 4 representing families.

Chylomicrons - S_f greater than 400

Pre - Beta - lipoproteins - S_f 21 - 400 (very low density)

Beta - Lipoproteins - S_f 0 - 20 (low density)

Alpha - Lipoproteins - High density

The chemical composition of major lipoproteins ; its relationship expressed by various methods and its normal value are shown in table I, II and fig. I. respectively.

CHYLOMICRONS : These large fat particles have a density of 0.9. They

are collected at top of plasma after left standing for 16 - 24 hours at 0 - 4° c. Most chylomicrons are considered to represent exogenous triglycerides and can cause cloudy appearance of the serum.

PRE - BETA - LIPOTROTEINS : These are very low density lipoprotiens (VLDL). Their density is less than 1.006. Pre-Beta-lipoproteins are apparently concerned mainly with the transport of endogenous triglycerides. It consists mainly of glycerides newly synthesized or derived from body store rather than directly from the diet. It seems possible that VLDL may be the only form in which lipoproteins are secreted by the liver and is not identical with those formed in circulation in the case of cholesteryl esters which are mainly synthesized by the plasma lecithin (4). It is also found that the lymph also contains VLDL synthesized by the intestine. In fasting stage, about half of lymph triglyceride and cholesterol is found in VLDL and these lipids are not derived from the plasma but from intestinal contents and mucosal synthesis (5).

BETA - LIPOPROTEINS : They are called low density lipoproteins (LDL) and can be isolated between the densities of 1.006 and 1 063 (S_f 0-20). Beta-lipoproteins appear to be the major transport medium for cholesterol. Their major constituents are cholesterol and cholesteryl ester ; the remaining components are phospholipids, protein and glyceride.

The composition of the S_f 0-20 lipoprotein contain 3 classes ; (6) HDL, LDL_3 and lipoprotein which shares antigenic determinant with LDL, LDL - a - l, HDL. Helenius and Simons (7) removed LDL by four different detergents and found that the lipid-free-proteins obtained still retained the immune properties.

ALPHA - LIPOPROTEINS (as more specifically Alpha $_1$-lipoprotein) : These are high density lipoproteins (HDL) being isolated at the densities of 1.063-1.21. They contain about 50 % of protein; lipid component consists mainly of cholesterol and phospholipids in the ratio of about 0.5 (by weight). It is now established that the mechanism of removal of lipoprotein and triglyceride by the enzyme, clearing-factor lipase (lipoprotein lipase); occuring at capillary cells and that the free fatty acids released then pass across the endothelail cells into the tissues. (8)

FREE—FATTY—ACIDS : Protein bound fatty acids or free fatty acids (FFA) that circulate are albumin bound. The normal concentration is 0.3 - 0.6 mEq/l with the average of 0.4 mEq/l. (9) They are important in meeting caloric demands and have most labile concentration. The FFA concentration is elevated in starva-

tion, excercise, emotional stress, low-tissue insulin activity and hyperthyroidism. Nicotine, caffeine and injection of epinephrine also raise the plasma FFA level. The effect is produced by the stimulation of lipolysis of triglyceride in adipose tissue.

The FFA level parallels the blood glucose level in diabetes, and in some ways is a better indication of the severity of the diabetic stage. (10) In diabetic acidosis, the level of FFA may rise to 1.5 mEq/l, returning to normal after successful treatment with insulin. The FFA released from adipose tissue in excess of those utilized by muscle, liver or other tissues mainly reappear in plasma as endogenous glyceride. The FFA may cause intravascular thrombosis, but this has been demonstrated only in very high concentrations.

BIOLOGICAL VARIATION : The fasting levels of the different plasma lipids, vary considerably between different individuals, population and also from hour to hour and day to day in one and the same individual.

Genetic, sex, age, diet, posture, venostasis, different environment, excercise, emotion, pregnancy and smoking pay influence in the plasma lipid levels. Taggart and Carruthers (11) showed that among racing drivers, free fatty acid levels were elevated for one to three minutes before the start and were maintained up to one hour after the race. The triglyceride levels were slightly elevated after the event and continued to increase and reached a peak at one hour.

CLASSIFICATION OF HYPERIPIDEMIA AND HYPERLIPOPROTEINEMIA

The proposed chemical classification provides and approach to the etiologic and to the pathogenetic factors of diseases.

HYPERLIPIDEMIA : This term refers to an increase in concentration of any plasma lipid constituents. For practical purpose, usually it is confined to cholesterol or glyceride or both.

The analysis of cholesterol and triglyceride also provide some information about the type of hyperlipoproteinemia because the proportion of these lipids varies from one lipoprotein family to another. Winkleman et al recommended that cholesterol and triglycerides should be routinely determined in the laboratory for testing of phenotyping of lipoproteinemia. The analysis must be performed in the same specimen to be run for electrophoresis in order to provide satisfactory accuracy. They could not classify a number of serum specimens because of the subjective interpretation of the positive and intensity of lipoprotein bands as due to the poor reproducibility and limited ability of the techinque to have a clear seperation between Beta and pre-Beta-bands. (12)

Three general types of hyperlipidemia that roughly coresponds to certain types of hyperlipoproteinemia are : -

1. High cholesterol concentrations and normal triglyceride concentrations - this group is also called " pure hypercholesterolemia ". It to corresponds to hyper - Beta - lipoproteinemia.

2. High cholesterol concentration and normal triglyceride concentration - this group usually corresponds to either " pure hyperchylomicronemia " or hyperpre-Beta-lipoproteinemia.

3. High cholesterol and high triglyceride concentrations - all of these major types of hyperlipoproteinemia, except "pure" hyper - Beta - lipoproteinemia, may occur in this group. The classification of this third group is based on types of lipoproteins.

HYPERLIPOPROTIENEMIA : For the sake of simplicity, the patterns or types of abnormal lipoproteins can be numbered according to the system of Fredrickson and colleagues, as shown in table III.

The plasma obtained from patient with either type I or type V hyperlipoproteinemias is characterized by a creamy layer separating over a clear (type I) or turbid (type V) plasma. Typer II, III, IV are characterized by a turbid plasma.

Typeo I and II_a are induced by fat feeding whereas type IV is carbohydrate induced. Typer II_b, III and V are induced by feeding both fat and carbohydrate.

Type I. Hyperchylomicronemia

Criteria : 1. Chylomicron present in excessive amount.

2. VLDL (pre-Beta-lipoprotein) normal or only slightly increased. This is partly due to the difficulty of separating these two lipoprotein families. The amount excess to VLDL, however, is always far less than overwhelming amount of chylomicrons (Alpha - Beta - lipoproteins are always decreased).

Type II. This type may be distinguished into two subtypes.

II_a only LDL (Beta-lipoprotein) is increased but

II_b both LDL (Beta-lipoprotein) and VLDL (pre - Beta - lipoprotein) are increased.

The presence of II_b in plasma may require additional treatment to that required for " pure " hypercholesterolemia.

In II_a plasma cholesterol is usually increased; plasma triglycerides are normal; cholesterol/triglyceride is always more than 1.5.

In II_b plasma cholesterol is usually increased ; plasma triglyceride is always increased; cholesterol/triglyceride is variable (not diagnostic). Alpha - lipoproteins are usually normal (diagnostic only if accompanied by estimation of LDL and

VLDL concentration).

Typer III. "floating Beta" or "broad Beta" pattern (lipoproteins of Beta mobility, floating at density of 1.006).

Criteria. Presence of "floating Beta" "Beta - (VLDL)" or with abnomal Beta-lipoprotein and abnormal high cholesterol.

Cholesterol / Triglyceride may vary from 0.3 to 2.0

Plasma triglycerides are (nearly) always increased.

Electrophoresis shows a "broad" band extending from the Beta position into the pre - Beta - position.

This type III lipoprotein may be suspected when a cholesterol/triglyceride ratio, especially when repeated analysis, shows marked lability of both cholesterol and triglyceride concentrations ; and a "broad Beta" band appears on conventional electrophoresis.

Type IV. Hyperpre-Beta-lipoproteinemia.

Criteria. 1. increased VLDL

2. no increase in LDL

3. chylomicron absent (diagnostic)

If the plasma cholesterol is difinitely normal, triglycerides are clearly increased and there no chylomicrons visible on standing plasma, the ascertainment of type IV is fairly certain. The accuracy is enhanced if electrophoresis reveals distict pre - Beta band and diminished Beta band.

Typet V. Hyperpre - Beta - lipoproteinemia and chylomiccronemia.

Criteria : 1. VLDL increased

2. Chylomicron present

Additional useful clinical data : Certian clinical findings are helpful in detecting hyperlipidemia and sometimes the prediction of the type of hyperlipoprotein can be made clinically.

e. g. Lipid deposit xanthomas, almost invariably, indicate hyperlipoprotein of long duration. They usually indicate hyper - Beta - lipoprotein and almost always imply to familial type II hyperlipoproteinemia.

Xanthelasma is frequent in type II and sometimes occurs in type III, but it may be seen in the bsence of hyperlipoproteinemia or hyperlipidemia.

Arcus cornea (arcus senilis) if occurs before the age of 40 years implies to f miiial type II hyperlipoproteinemia.

Pancreatitis or recurrent abdominal pain should lead to a suspicion of severe hyperglyceridemia (type I or V).

Ischemic heart disease and other vascular accidents in young relatives of the family with such diseases are usual in familial type II and type IV hyperlipoproteinemia.

(Diabetes is often seen in famlilies with type IV and type V hyperlipoproteinemia. In diabetic family, these disorders may occur long before the patient becomes diabetic).

The useful laboratory data are thyroid function, glucose tolerance, urinary protein; plasma protein lelectrophoresis, immune globulin quantification, liver fuction and uric acid.

Etiology of Hyperlipoproteinemia : When the pattern of hyperlipoproteinemia is established, the etiology must be considered whether it is primary or secondary hyperlipoproteinemia.

Secondary hyperlipoproteinemias are commonly associated with

1. Hypothyroidism
2. Diabetes
3. Nephrotic syndrome
4. Biliary obstruction
5. Pancreatitis
6. Dysglobulinemia including autoimmune hyperlipoproteinemia.

The lipoprotein patterns in such diseases are shown in the table IV.

Primary hyperlipoproteinemias are due to genetic defects in lipid or lipoprotein metabolism or to environmental factors through an unknown mechanism including diet or alcohol, and drugs causing hyperlipidemia e. g. steroids.

Familial hyperlipoproteinemias obviously need not be inheritable if it is due, for example, to pattern of excess in diet or alcohol intake that have been acquired by close relatives.

Clinical syndromes of hyperlipoproteinemias

Primary (Familial) type I.

The key clinical features of this familial syndrome are early expression of bouts of abdominal pain and other accompaniments of severe hyperlipemia low post heparin-lipolitic activity (PHLA) and autosomal recessive transmission. Yellow papules with reddish base may appear on the skin and oral mucosa. Liver and spleen are enlarged, while retinal vessels (lipemia retinalis) may be seen. Blood sample shows "creamy" appearance on the top. In children, if fat-free milk only is fed, the lipemia will be cleared dramatically within the day. The xanthoma will shortly resolve, the liver and spleen will decrease in size, abdominal discomfort, then, will disappear finally. In adults, sometimes the abdominal discomfort simulates immediate surgical conditions and undergoes unnecessary surgery.

In this type, oral or intravenous glucose tolerance shows no abnormality. This differs from other "fat-induced" type. (type IV and V).

Diagnosis can be made by the following steps :-

1. Identification of the type I lipoprotein pattern
2. Glyceride accumulation is immediately related to dietaty fat intake.
3. Plasma post heparin - activity (PHLA) is low

Type II. Hyperlipoproteinemia

High Beta-lipoprotein can be a resultant of diet or secondary to hypothyroidism and other diseases.

The second feature of type II pattern is associated with a modest increase in pre-Beta-lipoprotein. Femilial type II may be due to a mutation at the same genetic locus, heterozygote; xanthomatosis and atheromatosis are frequently seen.

Diagnosis. A triad for diagnosis is

1. Hyper-Beta-lipoprotein
2. Familial history of type II lipoproteinemia as an autosomal dominant trait.
3. Xanthomatosis

Practically (1) with (3) is adequate enough for diagnosis.

The most characteristic manifestation is tendinous xanthomas located particulary in the Achille tendons, and the extensor tendons of hands and feet. But important clinical features of familial type II are autosomal dominant and usually accompanied by palpebral, tendon and xanthomas, corneal arcus and accelerated arthero sclerosis. Glycerides (pre-Beta-lipoprotein) may be moderately elevated; PHLA is normal and glucose tolerance is usually normal.

Clofibate has less effect on plasma cholesterol in typer II, the most effective and least toxic agent is cholestyramine, a nonabsorbable exchange resin that stimulates cholesterol catabolism to bile salt by preventing their reabsorption from ileum. By using this drug, the rate of synthesis of cholesterol is less than that of catabolism, therefore, the net effect is the decrease of plasma cholesterol. Conversely in homozygote, cholestyramine does not decrease plasma cholesterol since the endogenous synthesis of cholesterol will increase to compensate for the increased catabolism to bile salt. An attempt to overcome the increased endogenous synthesis by nicotinic acid plus cholestyramine seems promising. (4)

Typer III. Excess of lipoprotein that has Beta mobility but abnormally low density manifests by hypercholesterolemia and hyperglyceridemia. The lipoprotein levels are quite sensitive to changes in the content of the diet and the amount of total calories. Polyunsaturated fat diet containing only 100-200 mg of cholesterol/day may lower both cholesterol and triglyceride concentrations for several fold in a few weeks. Carbohydrate intolerancerance is found in most patients.

Clinical manifestation besides arcus, palpebral and tendon xanthoma, there usually are palmar and tuberoeruptive xanthomas. Advanced arteriosclerosis of peripheral and coronary arteries is common. PHLA is normal; if familial, it is inherited as a recessive.

Primary type IV. This is the hallmark of endogenous hyperlipidemia. It implies that glycerides synthesized in the body, mainly in the liver have been excreted into plasma at the rate exceeding the capacity for removal. It often suggests that something has gone wrong with carbohydrate metabolism on caloric balance. It is sometimes called "carbohydrate-induced hyperlipemia". It is mainfested as hyper-pre-Beta lipoproteinemia associated with an increase in glycerides and commonly a rise in cholesterol; normal PHLA.

Severe type may show what described in exogenous hyperlipidemia. The patients are also subjected to develop bouts of abdominal pain with or without chemical signs of pancreatitis. Hyperuricemia is as common as glucose intolerance. Familial occurrence is seen in young children.

Secondary type IV. This can be seen in diabetes mellitus, pan-creatitis, glycogen-storage disease, idiopathic hypercalcemia, hypothroidism (but less common than type II, dysglobulinemia, pregnancy and contraceptive drugs).

Type V. This is a combination of both exogenous and endogenous hyperlipemia. The commonest complaint is recurrent abdominal pain but the symptom frequently appears in the late teen or third decade as compared to that occurs in infancy in type I. This is no relation to obesity or diabetes. PHLA is usually normal but may be somewhat lower. (In type I. distinctly low). Glucose tolerance is almost invariably abnormal. This pattern of hyperlipoproteinemia is often familial but there are "phenocopies" secondary to many disorders.

HYPERLIPOPROTEINEMIAS

Primary: These conditions are exceeding rare but have considerable importance.

Abetalipoproteinemia (Bassen-Kornzweig Syndrome). This disease, inherited as an autosomal recessive, is characterized by complete absence of LDL, VLDL and chylomicrons. It is manifested by severe malabsorption, beginning in early childhood, followed by progessive ataxia, nystagmus, weakness and visual impairment with scotomas. These are related, respectively, to inability to deliver triglycerides (due to absence of Beta-lipoprotein) into the intestinal lymph, demyelination of spinocerebellar tracts, posterior columns and occasionally peripheral nerves and pigmentary retinal degeneration (atypical retinitis pigmentosa). Other findings include thorny of spiny red cells (acanthocytes) and fatty liver (resulting from failure to export triglycerides in very low density lipoproteins)

This disease should be considered in any patient with hereditary ataxia. Treat-

ment is limited to restriction of ordinary fat and supplementation with fat soluble vitamins. Medium chain triglycerides are, however, well tolerated.

Alpha-lipoprotein Deficiency (Tangier disease). This is homozygous state leading to diffuse deposition of cholesterol esters in reticuloendothelial system with enlargement of the tissues, especially, the grossly enlarged tonsils (characteristic orange color). Foam cells may be found in the bone marrow. Usually the disorder does not affect growth. No treatment is available.

Lecithin - cholesterol Acyltransferase Deficiency. This disorder has been found in a Norwegian family. The effected subjects have proteinuria, anemia, and corneal deposits of lipid. HDL is almost absent with moderate to large elevations of VLDL and chylomicrons are present. Foam cells can be found in the bone marrow and renal glomeruli and increased concentration of cholesterol and lecithin in the red blood cells are also present.

Secondary : These states are characterized chiefly by hypobetalipoproteinemia and are the result of malnutrition, malabsorption, or parenchymal liver disease. Formation of LDL is decreased, presumably, due to decreased transport of exogenous and endogenous triglycerides. In healtly individuals whose intake of calories and saturated fats is low, the concentration of LDL are also decreased.

FIGURE I.

The p asma lipoprotein spectrum segregated by paper electrophoresis (above) and by the ultracentrifuge (below) in which S_f or floatation rates are inversely related to density.(2)

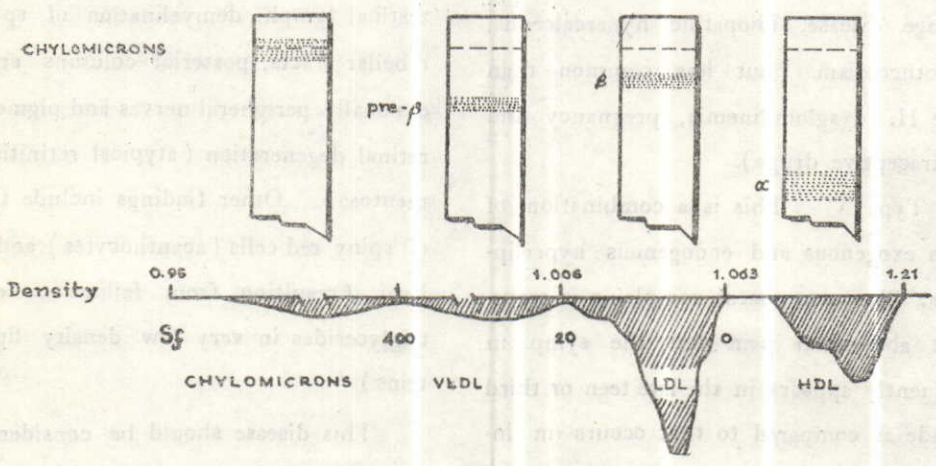

TABLE I.

Typical composition of major lipoproteins as expressed by percent of dry weight.

Lipoproteins	Protein	Triglyceride	Phospholipid	Cholesterol
Chyiomicrons	1.5 ± 1.0	87 ± 7	9 ± 6	7 ± 5
Pre-Beta	7 ± 5	65 ± 15	18 ± 8	16 ± 7
Beta	23 ± 3	10 ± 2	22	43
Alpha	50 ± 5	7 ± 2	30	18

(Adapted by Orten from data in Masoro, E.J.: Physiological Chemistry of Lipids in Mammals, Philadelphia, 1968, W.B. Saunders Co., Vol. I.)

TABLE II.

Suggested "Normal Limits" of plasma lipid and lipoprotein concentrations in normal subjects.

Age	Sex	Total Cholesterol	Triglyceride	Pre-Beta-lipo.	Beta-lipo.	Alph-lipo.	
						M	M
0-19		120-230	10-140	5-25	50-170	30-65	30-70
20-29		120-240	10-140	5-25	60-170	35-70	35-75
30-39		140-270	10-150	5-35	70-190	30-65	35-80
40-49		150-310	10-160	5-35	80-190	30-65	40-85
50-59		160-330	10-190	10-40	80-210	30-65	35-85

(For practical purpose differences between sexes have been ignored excepted of Alpha-lipoprotein concentrations).[3]

TABLE III.

The major abnormal lipoprotein pattern[a] and their type number.[2]

Type	Chylomicrons	LDL (Beta-lp	VLDL (pre-Beta-lp)	Floating Beta-lp[b]
I	+			
II_a		+		
II_b		+	+	
III				+
IV			+	
V	+		+	

a) Indicates which lipoprotein "family" (families) occurs in concentration above "normal" in the different abnormal patterns.

b) also know as "broad Beta-lipoprotein".

TABLE IV.

Types of hyperlipoproteinemia associated with selected common diseases:

Disorder	Type of Hyperlipoproteinemias
Hypothyroidism	II, IV
Insulin-dependent diabetes (uncontrolled)	I, IV, V (II, III)
Nephrotic Syndrome	II, IV, V
Biliary obstruction	Does not conform predictably to any of the major types
Pancreatitis	IV, V
Dysglobulinemia	I, II, IV, V, (III)
Auto-immune hyperlipoproteinemia	I, III, IV, V, (II)

REFERENCES

1. Orten, J.M ; Neuhaus, O W. ; Chemistry of Lipids. Biochemistry 269-291, Siant Louis, 1970, The C.V. Mosby Co.
2. Beaumont, J.L. et al : Classification of Hyperlipidemias and Hyperlipoproteinemias. Bull Wld. Hlth. Org., 43 : 891-908, 1970.
3. Fredrickson, D.S.; Levy, R.I. ; Lees, R.S. : Fat Transport in lipoprotein in an Intergrated Approach to Mechanism and disorders. New. Eng. J. Med. ; 276-151, Jan. 19, 1967.
4. March, J.B. Whereat, A. P. : Biosynthesis of Plasma Lipoproteins. J. Biol. Chem. 234 : 3169, 1959.
5. Issebacher, K.J. : The Intestine, Lipid Transport and Lipoproteins. Clin. Sci., 40 : 16P, April, 1971.
6. Alberts, J.J. ; Chen, C.H. ; Aludjim, F. : Human Serum Lipoproteins. Evidence for three Classes of Lipoproteins in S_f 0-2, Biochemistry, 11:57-63, Jan. 4, 72.
7. Helenius, A. ; Simons, K. : Removal of Lipid from Human Plasma Low-Density Lipoproteins by Detergents. Biochemistry, 10 : 2542-46, 1971.
8. Robinson, D. S. : The Mechanism of Removal of Lipoproteins, Triglyceride from the Plasma. Biochem. J. 123 : 20p-21p, Jul. 71.
9. Hoffman, W.S. : Lipids. The Biochemistry of Clinical Medicine, 158. 35 East Wacker Drive, Chicago, 1970, Year Book Medical Publishers. Inc.
10. Ganong, W. F. : Endocrine functions of the Pancreas and the Regulation of Caborhydrate Metabolism: Review of Medical Physiology, 280 - 281. Los Altos, California, 1969, Lange Medical Publication.
11. Taggart, P. ; Caruther, M. : Endogenous Hyperlipidemia Induced by Emotional Stress of Racing Driving. The Lancet, 1 : 363-365, Feb. 20, 1971.
12. Winkleman, J. ; Wybenga, D. R. ; Ibbott, F.A. . Correlation of Laboratory Tests and Clinical Evaluation in Phenotyping of Lipoproteinemias. 16 : 594-6, July, 1970.
13. Orlen, J.M. : Neuhaus, O. W. : Chemistry of Lipids. Biochemistry, 292-336, Saint Louis, 1970, The C. V. Mosby Co.
14. Ganong, W.G. : Fat Metabolism, Review of Medical Physiology, 244-250. Los Altos, California, 1969, Lange Medical Publication.
15. Neil, M.W. ; Lipid Metabolism. Basic Biochemistry, 246-262. Philadelphia, Montreal, 1960, J.B. Lippincott Co.
16. Beeson, P. B. and Mc Dermott, P. : Disorders of Lipid Metabolism. Cecil-Loeb Textbook of Medicine, 1667, Philadelphia - London - Toronto 1971. W. B. Saunders Co. Tokyo, 1971. Igaku Shoin Ltd.