MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

April 13, 1972

[Marvin D. Siperstein]

HYPERLIPEMIC STATES

Case 1: [redacted]

Severe Endogenous Hyperlipemia Causing Recurrent Pancreatitis

The patient is a 48 year old [redacted] woman who is employed as a secretary at [redacted]. In [redacted] of 1969 she experienced a sudden attack of mid-abdominal pain, amylase 540. On exploratory laparotomy acute pancreatitis was found. After discharge the patient returned to her usual diet, which emphasized steak, eggs, and butter. She thereafter continued to have attacks of severe abdominal pain at approximately monthly intervals until [redacted] 1970, when she was referred to Dr. Fordtran.

At that time lipemia retinalis and milky plasma were noted. A cholesterol of 344 and a triglyceride of 3,670 were obtained, and on refrigeration, plasma failed to show floatation of the fat particles. The absence of chylomicra was confirmed by electrophoretic pattern and the patient was diagnosed as having severe endogenous hyperlipemia. She was placed on a strict low carbohydrate, reduced calorie diet in which saturated fat was likewise avoided. On this diet the patient remained symptom-free for approximately one year. She then went off the diet, and within a few weeks, in [redacted], 1971, again had typical pancreatitis, requiring admission to Parkland. She thereafter returned to a relatively strict low saturated fat, low carbohydrate diet, and has had no further symptoms. Blood chemistries when seen on [redacted]/72 were cholesterol, 314 and triglyceride 55 mg/100 ml.

Case 2: [redacted] [redacted]

Endogenous Hyperlipemia Resulting in Pancreatitis and Hyperglycemia

The patient is a 31 year old alcoholic who was first seen in [redacted], 1970 with a two day history of progressively severe abdominal pain and serum amylase of over 1,000 units. On admission his plasma was noted to be markedly lipemic. Glucose was 250 mg%, cholesterol 522 mg%, triglyceride 2,300 mg%. The triglyceride did not float on standing overnight, and an electrophoretic pattern showed no evidence of chylomicra. The patient was treated conservatively with Pamine and nasogastric suction. Pancreatitis improved, triglyceride decreased to 285 mg%; however, his fasting blood sugar remained elevated at 178 mg% on discharge.

It is significant that the capillary basement membrane width was only 865 A, (diabetic > 1,600 A), a finding that would make the diagnosis of genetic diabetes mellitus very unlikely.

The patient was discharged on a high polyunsaturated fat, low carbohydrate, low calorie diet; however, after four months he was lost to followup. On [redacted]/70, his fasting blood sugar was 124 mg%, and his triglyceride, while improved, was still above normal at 493 mg%. He then discontinued his diet, and began drinking and on [redacted]/71 he was readmitted with a one day history of acute abdominal pain, a triglyceride of 1,293 mg%, cholesterol of 688 and glucose of 360 mg%. He was successfully treated with moderate amounts of insulin, was again placed on a low carbohydrate diet. On discharge his triglyceride was 225 mg%, cholesterol 125 mg%, and glucose 215 mg%.

In view of the normal capillary basement membrane width, the patient's primary disease is most likely endogenous hyperlipemia which, coupled with his alcoholism, has produced the recurrent pancreatitis, which in turn is probably responsible for his persistent hyperglycemia.

Case 3: [redacted] Private Patient

Fat-Induced Hyperlipemia Leading to Chylomicronemia, Probable Endogenous Lipemia and Pancreatitis

The patient is a 14 year old boy who gives a history of having repeated episodes of abdominal pain beginning at age 6 and recurring every two to three years thereafter. Exploratory laporotomy with first episode showed pancreatitis. In 1968 at age 13 he had a splenectomy following trauma to the left upper quadrant; at that time, milky plasma was first noted and the patient was placed on Atromid-S.

When first seen in Dallas, the patient gave a history of frequently eating fried fish sandwiches and fried chicken. His physical examination was completely unremarkable. However, laboratory values showed a triglyceride of 1,442 mg% and a cholesterol of 294 mg%, which is clearly elevated for a patient of age 14. The plasma was found partially to skim, but a definitely turbid infranate layer was also noted. The electrophoretic pattern showed definite chylomicra and there appeared to be a heavy pre-beta band. The patient was told to avoid eating fried fish sandwiches. A blood sample taken six weeks later showed a triglyceride of 196 mg% and a cholesterol value of 164 mg%.

Case 4: [redacted]

Exogenous (Fat-Induced) Hyperlipemia

The patient represents the only unequivocal example of fat induced hyperlipemia that we have seen at [redacted] in the past ten years. She is a 40 year old [redacted] woman who was first seen at [redacted] in [redacted] 1963 with the complaint of severe headaches, nuchal rigidity and projectile vomiting. These symptoms were regularly produced by eating any type of fatty food, but in particular, pork chops. The past history reveals frequent episodes of abdominal pain probably dating from childhood.

On admission the patient was somewhat drowsy; on funduscopic examination papilledema was present as well as typical lipemia retinalis. Eruptive xanthoma were noted over the left elbow; however, there was no hepatosplenomegaly. Serum was markedly lipemic. Cholesterol was 1,269 mg% and triglyceride 9,722 mg%. The patient was placed on NPO and maintained on intravenous fluid. Gradually over the next three days the lipemia cleared, and five days after admission the triglyceride had decreased to 488 mg% and the cholesterol, while still elevated, was 716 mg%. The patient was subsequently maintained on a relatively low fat, 30 gram diet, and both her cholesterol and triglyceride value returned to normal, and have remained so over the past nine years. When last seen on [redacted]/72 her triglyceride was 198 mg%, cholesterol 276 mg%.

Case 5: [redacted]

Mixed Hyperlipemia Mimicking Diabetes Mellitus

The patient is a 46 year old [redacted] woman who was admitted in [redacted], 1970 with a six month history of mid-abdominal pain diminished but not relieved by Maalox. Two weeks prior to admission polyuria and polydypsia were noted. The patient's past history was negative except for a bizaare history of drinking a total of 8-10 cups of coffee a day with Pream being substituted for cream. On the day prior to admission a large amount of pork was eaten. Examination was completely negative

except for nasal septal thinning suggestive of syphilis and minimal xanthoma tendonosum. Laboratory findings showed a glucose of 240 mg%; the plasma was definitely lipemic with a triglyceride of 2,930 mg% and a normal cholesterol, 143 mg%. No layering of the fat was detectable on refrigeration of plasma overnight. The initial blood sample showed a very faint chylomicron band; however, subsequent samples had no chylomicra despite a markedly elevated triglyceride. It was therefore concluded that the patient had a mixed type of hyperlipemia. Serum amylase was < 320. Capillary basement membrane proved to be well within the normal range, 919 A (diabetic level > 1,600 A), indicating that the patient's hyperglycemia was due to endogenous hyperlipemia rather than to diabetes mellitus.

The patient was discharged on a low calorie, low fat diet. By [redacted]/70 her triglyceride was decreased to 298 mg%; cholesterol 255 mg%; and glucose had returned to normal at 110 mg%. The patient's glucose has subsequently remained consistently normal without hypoglycemic therapy.

TABLES AND FIGURES

Table I

TRIGLYCERIDE LEVELS

1.	Statistical upper limit not well established Probably 250 - 300 mg/100 ml	
2.	Turbidity (fresh plasma)	400 mg/100 ml
3.	Turbidity (refrigerate overnight)	250 mg/100 ml
4.	Lipemia retinalis	3,000 mg/100 ml

Table 2

CAUSES OF ELEVATED CHOLESTEROL WITH CLEAR PLASMA

Secondary

1. Hypothyroidism
2. Biliary Cirrhosis
3. Early Nephrosis

Primary

1. Familial Hypercholesterolemia

Table 3

CAUSES OF HYPERLIPEMIA

Primary = Essential Hyperlipemia

1. Exogenous or fat-induced
2. Endogenous or carbohydrate-induced
3. Mixed

Secondary

1. Nephrotic syndrome
2. Alcoholism
3. Glycogen storage diseases
   a) Forbes-Cori
   b) von Gierke
4. Diabetes
   a) Acute ketoacidosis
   b) Poor control
5. Contraceptive pills
6. Pancreatitis ??

FIGURE 1

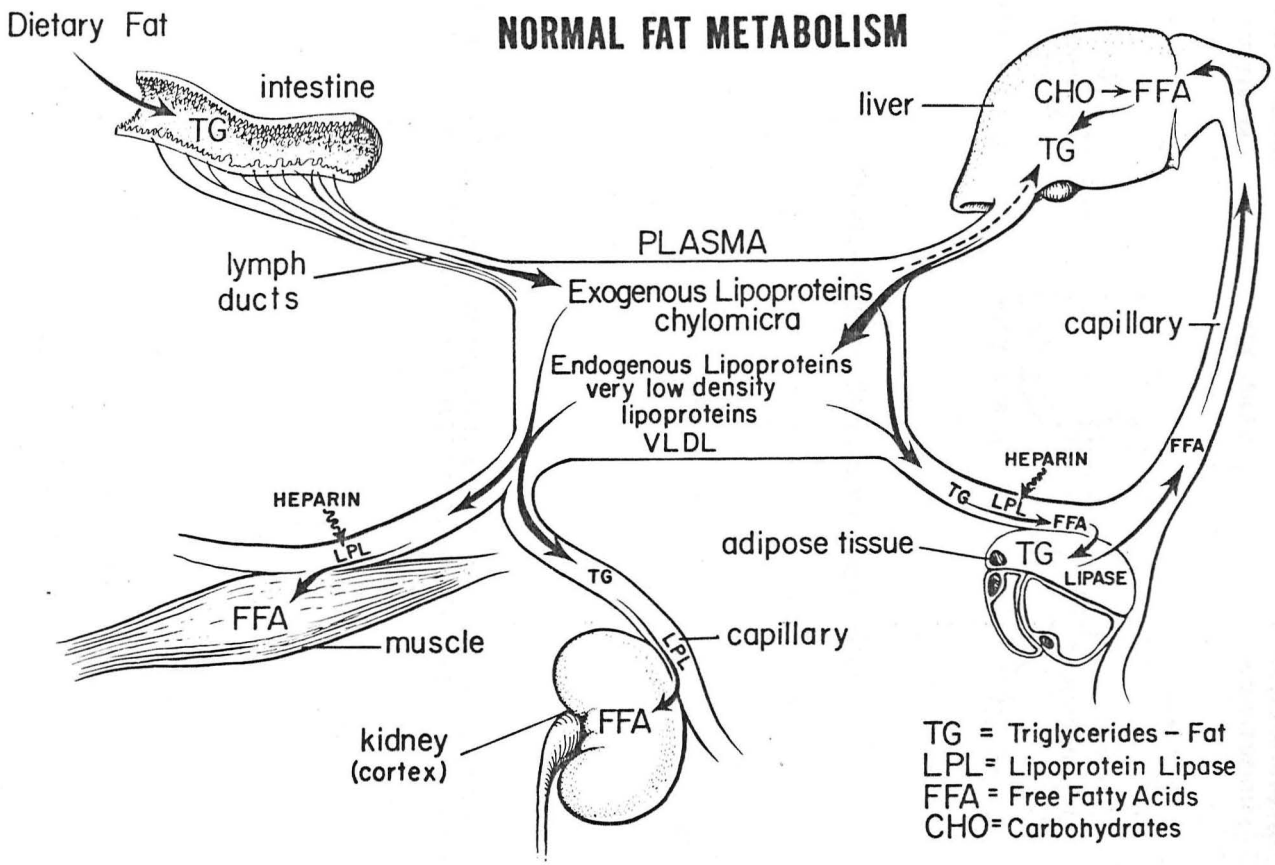
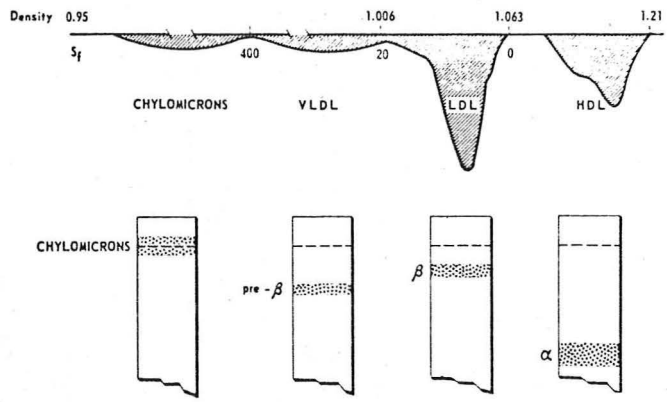

NORMAL FAT METABOLISM
Dietary Fat
intestine
TG
liver
CHO → FFA
TG
PLASMA
lymph ducts
Exogenous Lipoproteins chylomicra
Endogenous Lipoproteins very low density lipoproteins VLDL
capillary
HEPARIN
LPL
FFA
TG
adipose tissue
LIPASE
muscle
capillary
kidney (cortex)
TG = Triglycerides – Fat
LPL = Lipoprotein Lipase
FFA = Free Fatty Acids
CHO = Carbohydrates

FIGURE 2



THE PLASMA LIPOPROTEIN SPECTRUM AS SEGREGATED BY PAPER ELECTROPHORESIS (BELOW) AND BY THE ULTRACENTRIFUGE (ABOVE) IN WHICH S_f OR FLOTATION RATES ARE INVERSELY RELATED TO DENSITY.

FIGURE 3

CONVERSION OF VLDL TO β-LIPOPROTEIN

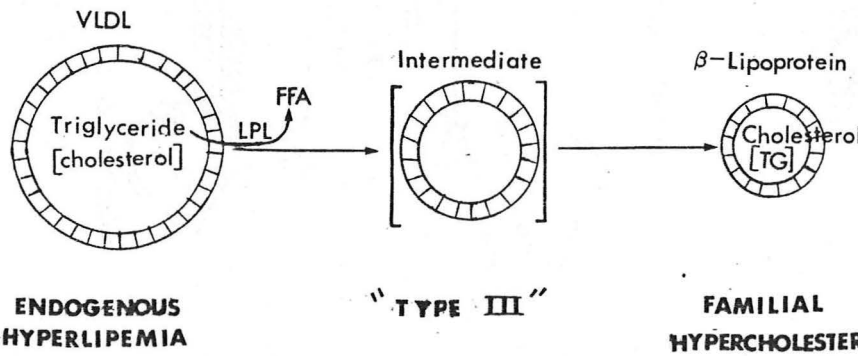


FIGURE 4

PROBABLE CAUSES OF TRIGLYCERIDE ACCUMULATION IN:

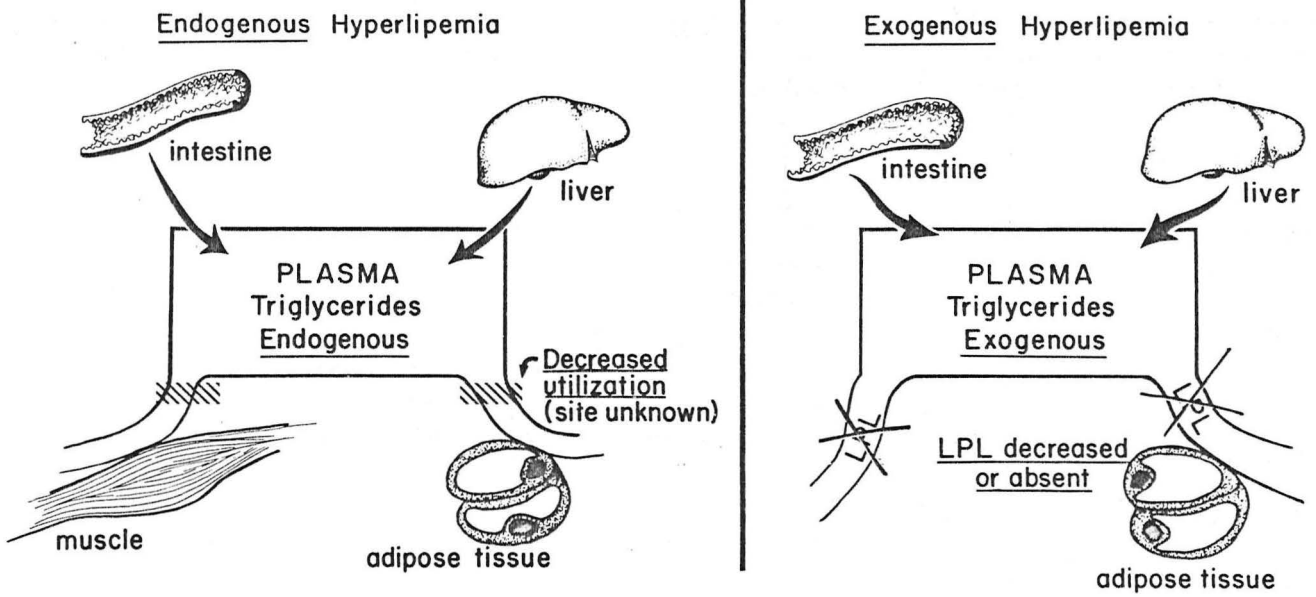
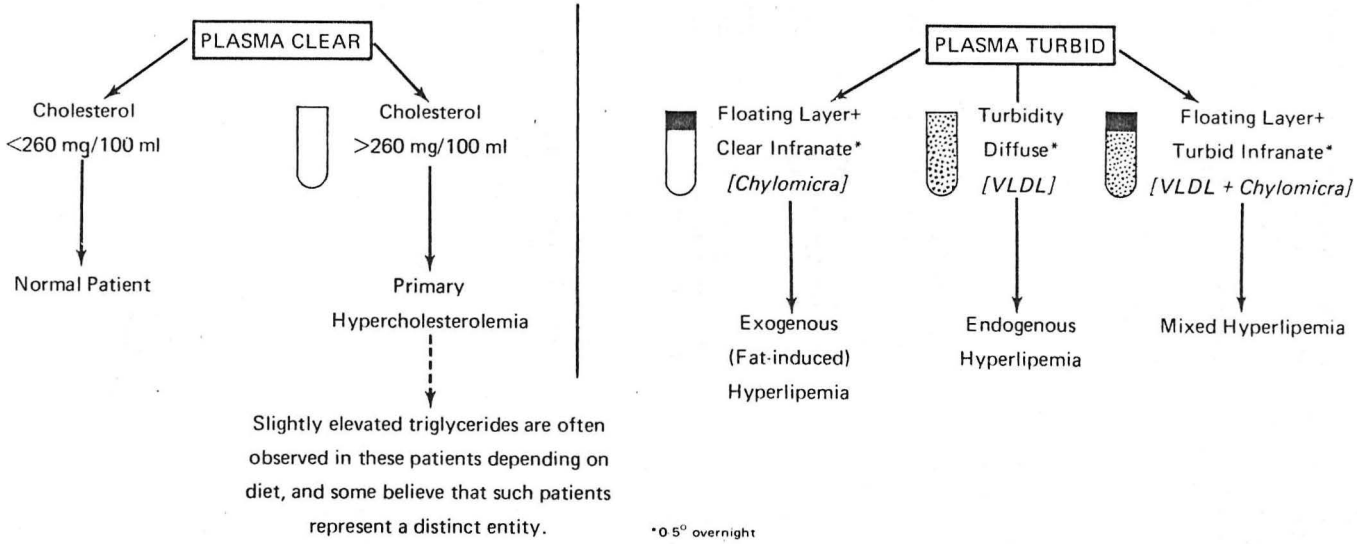


FIGURE 5

SCHEME FOR DIAGNOSIS OF PRIMARY HYPERCHOLESTEROLEMIC AND HYPERLIPEMIC STATES



*0 5° overnight

Table 4

SUMMARY OF DRUG THERAPY OF HYPERLIPIDEMIC STATES

	Mechanism	Comment
A. Familial Hypercholesterolemia		
1) Bile acid binding resins: Cholestyramine (Questran, Cuemid) Colestipol (16-24 gm/day)	Blocks absorption of exogenous and endogenous cholesterol	Safe and usually effective. May bind digitalis
2) Nicalex (Niacin 3 gm/day)	Blocks adipose tissue FFA release ultimately causing decreased β-lipoprotein synthesis by liver	Flushing and GI upset, rarely a serious problem
B. Endogenous Hyperlipemia		
1) Atromid-S (1.5 gm/day)	Decreases VLDL release (or synthesis) in the liver	Often, not always effective. Rare myositis, potentiates Coumarin
2) Nicalex (Niacin 3 gm/day)	Blocks FFA release thereby decreasing hepatic TG & VLDL synthesis	(see above)
3) Progestational Hormone	Unknown? May increase lipoprotein lipase	Experimental use in refractory cases
4) Bile acid binding resins raise triglyceride and are contraindicated		
C. Exogenous Hyperlipemia		
No drug effective		
D. Mixed Hyperlipemia		
1) Progestational hormones (Norlutate 5 mg/day)	Unknown	Experimental. May be very effective
2) Low fat diet (exogenous) + Atromid-S (endogenous)	Combined exogenous and endogenous therapy	---

FIGURE 6

SITES OF ACTION OF NICOTINIC ACID AND ATROMID-S

Table 5

UNSATURATED FAT CONTENT OF TYPICAL FOODS

Food	Total Fat (gm/100 gm)	Types of Fatty Acids (As Percent of Total Fatty Acids)	
		Saturated (Palmitic Stearic)	Polyunsaturated (Linoleic Linolenic Arachidonic)
Milk	4	63	2
Buttermilk	0.1	63	3
Butter	81	55-70	3
Egg Yolk	32	32	8
Swiss Cheese	28	60	2
Cottage Cheese	0.5	--	--
Chicken	13	30	20-30
Beef - Roast or Chuck	16-23	43	2
Veal Cutlet	9	52	7
Pork - Bacon	65	34	2-3
Ham	31	35	8
Liver	3	36	20
Lamb Chop	32	49	6
Salmon	16	17	50-65
White Fish	7	24	24
Trout	4	24	43
Tuna	8	26	54
Olive	--	9	5
Coconut	35	91	1
Cocoa	--	60	2
Almonds	54	9	21
Peanuts	44	21	25
Pecans	73	11	22
Walnuts	60	7	65
Corn Oil	90	12	57
Cottonseed Oil	90	26	52
Safflower Oil	90	8	72
Hydrogenated Shortening	80	38	7
Fleischman's Margarine	80	7	10
Mazola Margine	80	18	28
Chiffon Margine	80	13	63
"Diet" Chiffon Margarine	40	15	52

GENERAL REVIEWS OF HYPERLIPEMIC STATES

1) Havel, R. J. Pathogenesis, differentiation and management of hypertriglyceridemia. In Advances in Internal Medicine, Vol. 15, Stollerman, G., ed., Chicago, Yearbook Medical Publishers, 1969, p. 117.

The most balanced overall review of hyperlipemic states to date.

2) Fredrickson, D. S. and Levy, R. I. Familial hyperlipoproteinemia. In The Metabolic Basis of Inherited Disease, Stanbury, J., Wyngaarden, J. and Fredrickson, D., eds., 3rd ed., New York, McGraw-Hill, Inc., 1972, p. 545.

A good review of primary hypercholesterolemia and the hypertriglyceridemic states slanted toward the authors' classification of hyperlipidemic states using paper electrophoresis.

3) Frantz, I. D., Jr. and Moore, R. B. The sterol hypothesis in atherogenesis. Amer. J. Med. 46:684, 1969.

A brief review of the relation of triglyceride and cholesterol to atherogenesis.

4) Fredrickson, D. S., Levy, R. I., and Lees, R. S. Fat transport in lipoproteins - an integrated approach to mechanisms and disorders. New Eng. J. Med. 276:32, 1967.

A complete review of the authors' patients, which are probably highly selective.

5) Hollenberg, C. H. Regulation and clinical significance of serum triglyceride values. Trans. Asso. Life Insurance Medical Directors of Amer. 53:68, 1970.

Good brief overview of hyperlipemic states.

6) Stone, N. J. and Levy, R. I. Hyperlipoproteinemia and coronary heart disease. Prog. in Cardiovas. Dis. 15:341, 1972.

The latest review of the concepts of diagnosis and treatment from the NIH studies.

ENDOGENOUS HYPERLIPEMIA

Clinical

7) Ahrens, E. H., et al. Carbohydrate induced and fat induced lipemia. Trans. Assoc. Amer. Phys. 74:134, 1961.

AND

8) Ahrens, E. H., and Spritz, N. Further studies on fat and carbohydrate induced lipemia in man. Reduction of lipemia by feeding fat. In Biochemical Problem of Lipids. New York, Elsevier Co., 1965, p. 304.

First clear separation of endogenous (carbohydrate induced) and exogenous (fat induced) hyperlipemia.

9) Havel, R. J. Reference 1.

and

10) Fredrickson, D. S., et al. References 2 and 4.

The major reviews of endogenous hyperlipemia.

Metabolic Defect in Endogenous Hyperlipemia

11) Reaven, G. M., et al. Kinetics of triglyceride turnover of very low density lipoproteins of human plasma. J. Clin. Invest. 44:1826, 1965.

Concludes that increased production of triglycerides by liver is the cause of endogenous hyperlipemia.

12) Sailer, S., Sanhofer, F., and Braunsteiner, H. Umsatzraten fur freie Fettsauren und triglyceride im plasma bei essentieller hyperlipamie. Klinische Wochenschrift 44:1032, 1966.

The first good evidence that the defect in endogenous hyperlipemia is due to underutilization of VLDL.

13) Havel, R. J. Reference 1, p. 135.

Confirm Sailer that a limited rate of utilization is the probable primary defect in endogenous hyperlipemia.

14) Bilheimer, D., Eisenberg, S., and Levy, R. I. Human plasma very low density lipoprotein (VLDL) metabolism. J. Clin. Invest. 50:8a, 1971 (Abstract).

The first direct evidence that VLDL is converted unidirectionally to LDL by lipolysis.

Carbohydrate Intolerance in Endogenous Hyperlipemia

15) Knittle, J. L. and Ahrens, E. H., Jr. Carbohydrate metabolism in two forms of hyperglyceridemia. J. Clin. Invest. 43:485, 1964.

Insulin response to tolbutamide was decreased in carbohydrate-induced hyperlipemias.

16) Fredrickson, D. S. Reference 2

Carbohydrate intolerance is a common finding in endogenous (Types III & IV).

17) Bierman, E. L. and Porte, D. Carbohydrate intolerance and lipemia. Ann. Int. Med. 68:926, 1968.

18) Havel, R. J. Reference 1

Decreased glucose tolerance is an almost constant finding in hyperlipemia.

19) Siperstein, M. D., Unger, R. H., and Madison, L. L. Studies of muscle capillary basement membranes in normal subjects, diabetic and prediabetic patients. J. Clin. Invest. 47:1973, 1968.

The hyperglycemia that accompanies hyperlipemia is usually not due to diabetes mellitus but is a 2° form of hyperglycemia.

Treatment of Endogenous Hyperlipemia

20) Lees, R. S. and Wilson, D. E. The treatment of hyperlipidemia. New Eng. J. Med. 284:186, 1971.

Excellent review of therapy of all hyperlipemic states.

Caloric and especially carbohydrate restriction in diet and weight loss are all critical.

1. Decreased dietary carbohydrate intake will decrease triglyceride synthesis from carbohydrate in liver.

   21) Ahrens, E. H., et al. References 7 and 8.

2. Fatty acids released from adipose tissue contribute to hepatic triglyceride synthesis. Decreasing adipose tissue will decrease free fatty acid release and so decrease "triglyceride synthesis".

   22) Nestel, P. J. and Whyte, H. M. Plasma free fatty acid and triglyceride turnover in obesity. Metabolism 17:1122, 1968.

3. Drug and Surgical Treatment - See Below

The Apparent Prevalence of Endogenous Hyperlipemia is Suspiciously High

By electrophoresis:

23) Besterman, E. M. M. Liproteins in coronary artery disease. Brit. Heart J. 19:503, 1957.

99% of post-MI patients had pre-β band and assumed disease.

But

24) Smith, E. B.. Lipoprotein patterns in myocardial infarction. Lancet II:910, 1957.

Found pre-βeta band in 70% of normal men over 50 years.

By triglyceride analysis:

25) Brown, D. F., Kinch, A. S. and Doyle, J. T. Serum triglycerides in health and in ischemic heart disease. N. Eng. J. Med. 273:947, 1965.

55% of men with ischemic heart disease have triglycerides greater than "normal" 180 mg/100 ml.

BUT

42% of normal men exceeded the upper limit of "normal".

Similarly, in a Larger Group of Subjects

26) Brown, D. F. and Doyle, J. T. Pre-Beta Lipoproteinemia. Its bearing on the dietary management of serum lipid disorders as related to ischemic heart disease. Amer. J. Clin. Nutrition 20:324, 1967.

56% of men with ischemic heart disease had triglycerides over 180 mg/100 ml, and 53% of controls exceeded this value.

27) Wood, P., et al. The prevalence of plasma lipid abnormalities in men and women of the central valley, California. J. Clin. Invest. 50:99a, 1971.

Only survey of lipid levels in population survey (998 subjects). Even using a triglyceride level of 200 mg/100 ml as the upper limit, 22% of men age 50-59 were said to have endogenous hyperlipemia.

"FLOATING β, "BROAD β" OR TYPE III HYPERLIPEMIA

28) Fredrickson, D. S. and Lees, R. S. Familial hyperlipoproteinemia, In The Metabolic Basis of Inherited Disease, Vol. 2, Stanbury, Wyngaarden, and Fredrickson, eds. New York, McGraw-Hill, 1966, p. 429.

Redefined Gofman's 1954 description of "xanthoma tuberosum" as broad beta disease.

29) Fredrickson, D. S. Reference 4.

Introduced floating beta as definition of Type III.

30) Borrie, P. Type III hyperlipoproteinaemia. Brit. Med. J. 2:665, 1969.

The largest series of "Type III" hyperlipoproteinemia patients (Fredrickson described clinical features of eight cases) illustrates well the difficulty of establishing this diagnosis, which here is made on the basis of tuberous xanthoma in presence of elevated triglyceride levels.

Defect in Type III Hyperlipemia

31) Hazzard, W. R., Porte, D., Jr., and Bierman, E. L. The abnormal lipoprotein of broad beta disease. Clin. Res. 16:344, 1968.

AND

32) Quarfordt, S., Levy, R. I. and Fredrickson, D. S. On the lipoprotein abnormality in Type III hyperlipoproteinemia. J. Clin. Invest. 50:754, 1971.

Noted floating beta has a high cholesterol:triglyceride ratio and probable primary protein alterations.

Type III and IV Occur in Siblings in Same Family

33) Fredrickson, D. S. and Levy, R. I. Reference 2.

Electrophoretic patterns of Type III and IV can be interchanged by diet.

34) Jepson, E. M., et al. Treatment of essential hyperlipidaemia. Lancet 2:7634, 1969.

Type III is converted to Type IV on low carbohydrate diet. Xanthoma is not specific for either type.

35) Polano, M. K., Baes, H., Hulsmans, A., Querido, A., Pries, C., and van Gent, C. Xanthomata in primary hyperlipoproteinemia. Arch. Derm. 100:387, 1969.

Xanthoma of Type III are not specific, seen equally in Type IV, e.g. palmar xanthoma and xanthoma tuberosum present with equal frequency in Type II, III, and IV.

36) Wood, P., et al. Reference 27.

Prevalence of Type is only 0.2%.

EVIDENCE FOR AND AGAINST TRIGLYCERIDES BEING A RISK FACTOR IN ATHEROSCLEROSIS

37) Albrink, M. J., Meigs, J. W. and Man, E. B. Serum lipids, hypertension and coronary artery disease. Amer. J. Med. 31:4, 1961.

First to show a relationship between coronary disease and triglyceride (and cholesterol) levels. But elevated triglycerides could have been due to inclusion of recent MI patients.

38) Carlson, L. A. Serum lipids in men with myocardial infarction. Acta Med. Scand. 167, fasc. 6:399, 1960.

Cholesterol alone or triglyceride alone is elevated in about one-fourth of post-M.I. patients, suggesting triglyceride is a risk factor.

39) Hayes, D. and Neil, D. Serum cholesterol and triglycerides in ischaemic heart disease. Clin. Sci. 26:185, 1964.

In post-M.I. patients, triglyceride alone is elevated (22%) more often than cholesterol (14%), but cholesterol and triglyceride are both increased in approximately 20%.

40) Brown, D. F., Kinch, S. H. and Doyle, J. T. Serum triglycerides in health and in ischemic heart disease. New Eng. J. Med. 273:947, 1965.

Tried to dissociate triglyceride and cholesterol elevations as risk factors in MI in 2,000 patients. Both cholesterol and triglyceride are independent risk factors but cholesterol is more potent. Nonetheless, a high triglyceride is clearly correlated with premature atherosclerosis, especially in young men.

Triglyceride per se is probably far less atherogenic than cholesterol

41) Stamler, J. Nutrition, metabolism and atherosclerosis. In Controversy in Internal Medicine, Ingelfinger, Relman and Finland, eds, Philadelphia, W. B. Saunders Co., 1966, p. 27.

And

42) Stamler, J. Lectures on Preventive Cardiology. New York, Grune and Stratton, Inc., 1967. P. 107.

Concludes that there is no good evidence that plasma triglyceride is as atherogenic as is cholesterol.

43) Kannel, W. B., et al. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: The Framingham Study. Ann. Int. Med. 74:1, 1971.

Latest and final compilation of Framingham data - cholesterol levels in prospective study were best correlated with risk of subsequent coronary heart disease even in patients with elevated triglyceride or pre-beta lipoproteinemia. In men, pre-beta lipoprotein determination added nothing to prediction of subsequent MI.

44) Gofman, J. W., Young, W. and Tandy, R. Ischemic heart disease, atherosclerosis, and longevity. Circulation 34:679, 1966.

Even by ultracentrifugation, lipoprotein determination is probably no better than total cholesterol in determining risk of MI.

EXOGENOUS (FAT-INDUCED) HYPERLIPEMIA

Metabolic Defect

45) Havel, R. J. and Gordon, R. S., Jr. Idiopathic hyperlipemia: Metabolic Studies in an affected family. J. Clin. Invest. 39:1777, 1960.

First to distinguish exogenous hyperlipemia as an entity on the basis of post-heparin plasma LPL deficiency.

46) Harlan, W. R. Jr., Winesett, P. S., and Wasserman, A. J. Tissue lipoprotein lipase in normal individuals and in individuals with exogenous hypertriglyceridemia and the relationship of this enzyme to assimilation of fat. J. Clin. Invest. 46:239, 1967.

Lipoprotein lipase is present in normal human adipose tissue but markedly depressed in patients with exogenous hyperlipemia. LPL is normal in patients with endogenous hyperlipemia.

47) Herbert, P., et al. On the lipolytic defect in familial Type I hyperlipoproteinemia. J. Clin. Invest. 50:44a, 1971 (abstract).

Clearly demonstrates that patients with exogenous hyperlipemia lack LPL from adipose tissue. A second LPL derived from liver is normal, explaining some of the confusion of earlier studies.

Clinical

48) Ahrens, E. H. References 7 and 8.

The first to distinguish exogenous hyperlipemia on the basis of response to dietary fat.

49) Havel, R. J., Reference 1; Frederickson, D. S., Reference 2.

Remain the best descriptions of this very rare entity.

Heparin Binding as a Cause of Exogenous Hyperlipemia

50) Glueck, C. J., et al. Acquired Type I hyperlipoproteinemia with systemic lupus erythematosus, dysglobulinemia and heparin resistance. Amer. J. Med. 47:318, 1969.

Note coagulation defect and chylomicra in one patient with lupus.

51) Glueck, C. J., et al. A new mechanism of exogenous hyperglyceridemia. Ann. Int. Med. 71:1051, 1969.

Systemic lupus and lymphoma can lead to chylomicronemia. Low LPL due to binding of endogenous heparin to immunoglobulin is the probable cause. Finding provides strong evidence for the normal role of endogenous heparin in triglyceride metabolism.

FREDRICKSON TYPING - BASED ON PAPER ELECTROPHORESIS OF LIPOPROTEINS

Current Evaluation

"Electrophoresis is placed in proper perspective as being, by itself, *rarely specific, and sometimes misleading*".

Fredrickson, Ann. Int. Med. 75:471, 1971

52) Smith, E. B. Lipoprotein patterns in myocaridal infarction. Lancet 2:910, 1957.

and

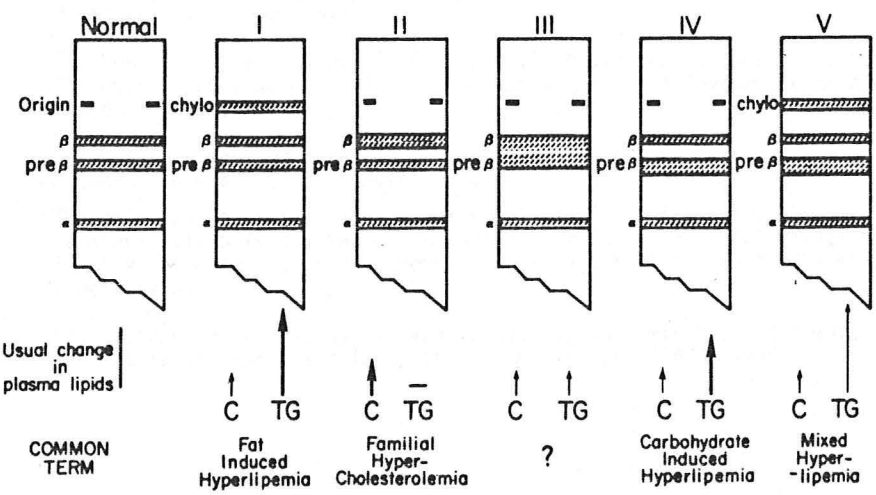
52a) Lees, R. S. and Fredrickson, R. S. Use of paper electrophoresis in the diagnosis and study of hyperglyceridemia. Circulation 30(suppl. 3):20, 1964.

The two studies describing use of paper electrophoresis to detect clinical lipoprotein disorders.

53) Fredrickson, D. S., Levy, R. I. and Lindgren, F. T. A comparison of heritable abnormal lipoprotein patterns as defined by two different techniques. J. Clin. Invest. 47:2446, 1968.

The only definitive study attempting to evaluate the paper electrophoresis method against ultracentrifugation. The two methods agree but only five samples from selected subjects comprise the study.

LIPOPROTEIN PATTERNS IN FAMILIAL HYPERLIPOPROTEINEMIA ACCORDING TO FREDRICKSON



Disadvantages

1. Cannot and does not measure lipoproteins (although most papers and laboratory reports falsely imply that lipoproteins are measured, there is no procedure available for accurately quantitating lipoproteins by paper electrophoresis).

2. Is not even quantitative for lipids.

3. Only practical purpose is to determine qualitatively if chylomicra are responsible for the cloudy serum, i.e. in a patient with demonstrated elevation of triglyceride. In our experience, and Havel's (Ref. 1), this is more easily done by looking at plasma after sitting.

4. Of no diagnostic value in patients with clear plasma even if cholesterol is elevated.

5. Repeated analyses do not check.

   54) Jepson, E. M., et al. Treatment of essential hyperlipidaemia. Lancet 2:7634, 1969.

6. Readings of same analysis by different observers in a good lipid laboratory demonstrated marked disagreements in diagnosis.

   55) Pries, C., et al. Primary hyperlipoproteinemia: the clinico-chemical classification of the most common types. Clin. Chim. Acta 19:181, 1968.

   Five observers read twenty electrophoretic patterns; all agreed on the diagnosis in only six patients.

   56) Lehmann, H. and Lines, J. G. Hyperlipoproteinaemia classification: The optimum routine electrophoretic system and its relevance to treatment. Lancet 1:557, 1972.

   While supporting use of paper electrophoresis, authors emphasize that staining is not constant and treatment obscures diagnosis.

7. The only quantitative study of the relationship of lipoproteins per se to atherosclerosis has indicated that determination of total cholesterol is as valid a predictor of atherosclerosis as is measurement of specific lipoproteins.

   57) Gofman, J. W., Young, W. and Tandy, R. Ischemic heart disease, atherosclerosis and longevity. Circulation 34:679, 1966.

DRUG TREATMENT

ATROMID-S

The Early Evidence that Atromid-S Lowers Serum Cholesterol:

58) Hellman, L., et al. Reduction of cholesterol and lipids in man by ethyl p-chlorophenoxyisobutyrate. Ann. Int. Med. 59:477, 1963.

and

59) Oliver, M. F. Further observations on the effects of Atromid and of ethyl chlorophenoxy-isobutyrate on serum lipid levels. J. Athero. Res. 3:427, 1963.

Current Status:

1. Often effective in endogenous hyperlipemia and in mixed hyperlipemia (with low fat diet).

2. No evidence of any significant effect on cholesterol levels in familial hypercholesterolemia.

60) Spritz, N. Effects of ethyl-α-p-chlorophenoxyisobutyrate (CPIB) on endogenous hyperglyceridemia (P). Circulation Suppl. 2:201, 1965.

61) Oliver, M. F. The present status of clofibrate. Circulation Suppl. 1:201, 1965.

62) Oliver, M. F. The primary prevention of ischemic heart disease by means of Atromid-S (Clofibrate). Bulle. N. Y. Acad. Med. 44:1021, 1968.

63) Levy, R. I., et al. The efficacy of clofibrate (CPIB) in familial hyperlipoproteinemias. In Drugs Affecting Lipid Metabolism, Plenum Press, 1969, p. 377.

Effect in familial hypercholesterolemia is no more than 9%, but none of the above four papers (References 60-63) incorporates control patients.

64) Hagopian, M. and Robinson, R. The effect of chlorophenoxyisobutyrate on plasma composition of cholesteryl esters and on levels of neutral lipids.

and

65) Danowski, T. S., et al. Hypolipidemic effect of chlorophenoxyisobutyrate in adult-onset diabetes mellitus. Clin. Pharm. Therapeutics 7:631, 1966.

Two of the many uncontrolled studies of Atromid-S claiming decrease in serum cholesterol.

66) Krasno, L. R. and Kidera, G. J. Clofibrate in coronary heart disease. J.A.M.A. 219:845, 1972.

Hypolipidemic effect is probably insignificant in absence of hyperlipemia - no control data are present. But report new MI's are markedly reduced by Atromid-S, 5.0/100/yr versus 0.64/1000/yr in treated group.

67) Strisower, E. H., Adamson, G. and Strisower, B. Treatment of hyperlipidemias. Amer. J. Med. 45:488, 1968.

Atromid-S is usually effective in endogenous hyperlipemia.

Mechanism of Action

68) Azarnoff. D. L., Tucker, D. R., and Barr, G. A. Studies with ethyl chlorophenoxyisobutyrate (clofibrate). Metabolism 14:959, 1965.

Atromid-S probably acts by decreasing triglyceride production by liver.

NICOTINIC ACID

Current Status:

Remains a very effective hypolipemic, hypercholesterolemic agent. Dose 1 gm t.i.d.

69) Altschul, R. Niacin in Vascular Disorders and Hyperlipemia. Springfield, Charles C. Thomas Co., 1965.

Niacin will lower both cholesterol and triglyceride in hypercholesterolemic and hyperlipemic states.

70) Christensen. N. A., et al. Hypercholesteremia: Effects of Treatment with nicotinic acid for three to seven years. Dis. of the Chest 46:411, 1964.

Niacin effect on cholesterol persists for at least seven years.

Mechanism of Action

71) Carlson, L. A. and Oro, L. The effect of nicotinic acid on the plasma free fatty acids. Acta Med. Scand. 172:641, 1962.

Nicotinic acid inhibits adipose tissue lipase and decreases the release of free fatty acids.

72) Carlson, L. A., Oro, L. and Ostman, J. Effect of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia during the first week of treatment. J. Atheroscler. Res. 8:667, 1968.

Sequence of oral nicotinic acid action in man is:

Lowers free fatty acids in minutes and lasts 3 hours.
Lowers triglyceride in 4 to 6 hours.
Lowers cholesterol only after 4 days.

73) Miettinen, T. A. Effect of nicotinic acid on catabolism and synthesis of cholesterol in man. Clin. Chim. Acta 20:43, 1968.

Nicotinic acid causes an increased excretion of endogenous cholesterol without increase in cholesterol synthesis. Presumably therefore nicotinic acid mobilizes cholesterol stores.

BILE ACID BINDING RESINS

Current Status:

Totally ineffective in hyperlipemic states (very effective in familial hypercholesterolemia).

74) Hashim, S. A. and Van Itallie, T. B. Cholestyramine resin therapy for hypercholesterolemia: Clinical and metabolic studies. J.A.M.A. 192:289, 1965.

and

75) Howard, R. P., Brusco, O. J. and Furman, R. H. Effect of cholestyramine administration on serum lipids and on nitrogen balance in familial hypercholesterolemia. J. Lab. Clin. Med. 68:12, 1966.

Bile acid binding resin is often, not always, effective in familial hypercholesterolemia.

76) Fallon, H. J. and Woods, J. W. Response of hyperlipoproteinemia to cholestyramine resin. J.A.M.A. 204:1161, 1968.

Cholestyramine is effective in familial hypercholesterolemia, but ineffective if triglycerides are elevated, i.e. endogenous hyperlipemia. No effect on triglycerides in any disease.

77) Caldwell, J. H. and Greenberger, N. J. Cholestyramine enhances digitalis excretion and protects against lethal intoxication. J. Clin. Invest. 49(6): 16a, 1970.

Cholestyramine binds digitalis in the intestine. Due to enterohepatic circulation of digitalis, cholestyramine will reverse toxicity and effectiveness of usual dosage.

PROGESTATIONAL HORMONES IN TREATMENT OF HYPERLIPEMIA

Current Status:

Experimental but look promising.

78) Glueck, C. J., et al. Amelioration of hypertriglyceridaemia by progestational drugs in familial Type V hyperlipoproteinaemia. Lancet 1(7609):1290, 1969.

Four patients with mixed hyperlipemia, Type V, improved on treatment with progestational hormones (2-10 fold decreases in triglycerides).

79) Glueck, C. J., Levy, R. I., and Fredrickson, D. S. Norethindrone acetate, postheparin lipolytic activity and plasma triglyceride in familial Types I, III, IV, and V hyperlipoproteinemia. Ann. Int. Med. 75:345, 1971.

Types III, IV, and V will each respond to progestational hormones.

ILEAL BYPASS - BUCHWALD PROCEDURE

80) Buchwald, H. Lowering of cholesterol absorption and blood levels by ileal exclusion. Circulation 29:713, 1964.

Claim ileal bypass lowers cholesterol in four patients. No data given.

81) Buchwald, H. The effect of ileal bypass on atherosclerosis and hypercholesterolemia in the rabbit. Surgery 58:22, 1965.

Atherosclerosis in cholesterol fed rabbits is prevented by ileal diversion.

82) Buchwald, H., et al. Five years experience with the use of partial ileal bypass in the treatment of hypercholesterolemia and atherosclerosis. Israel J. Med. Scien. 5:760, 1969.

Preliminary report of first fifty patients with ileal bypass. Claim 45% decrease in cholesterol and subjective clinical improvement noted. No data are presented. Cholesterol synthesis increased over four-fold.

83) Buchwald, H. Ileal bypass in the treatment of the hyperlipidemias. J. Atheroscler. Res. 10:1, 1969.

An editorial reviewing results. B-12 deficiency is a constant feature.

84) Moore, R. B., et al. Partial ileal bypass: a clinical appraisal of the Minnesota study. Circulation 44:47, 1971 (Abstract).

Brief summary of latest result of ileal bypass. Five year followup of 100 hypercholesterolemic and hyperglyceridemic patients showed 41% reduction in cholesterol, 346 → 209 mg%. Endogenous hyperlipemia said to respond as well, 40-60% reductions. No data.

85) Dietschy, J. M. and Siperstein, M. D. Cholesterol synthesis by the gastrointestinal tract: localization and mechanisms of control. J. Clin. Invest. 44:1311, 1965.

Bile diversion increases intestinal cholesterol synthesis.

86) Moutafis, C. D. and Myant, N. B. Increased hepatic synthesis of cholesterol after ileal by-pass in monkeys. Clin. Scien. 34:541, 1968.

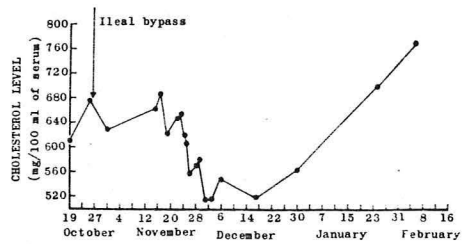
Bile diversion increases hepatic cholesterol synthesis.

87) Johnston, Ivan, et al. Ileal by-pass in the management of familial hypercholesterolaemia. Proc. R. Soc. Med. 60:746, 1967.

and

88) Davis, J., et al. Ileal bypass in hypercholesterolaemia. Lancet, Oct. 29, 1966, p. 971.

Ileal bypass caused transient decrease, then marked increase in plasma cholesterol.



CONCLUSION: Despite striking claims, after nine years of use no definitive data on the results of this procedure have yet been published (1972).

GENETIC DIABETES MELLITUS AND HYPERLIPEMIA

Diabetics usually have normal plasma lipids:

89) New, M.I., et al. The significance of blood lipid alterations in diabetes mellitus. Diabetes 12:208, 1963.

No difference in triglyceride levels between normal and diabetic patients until at least age 50 years. No correlation between complications of diabetes and blood lipids.

High carbohydrate diets will cause increase in plasma triglycerides in diabetics just just as in normal subjects:

90) Bierman, E. L. and Hamlin, J. T. The hyperlipemic effect of a low-fat, high carbohydrate diet in diabetic subjects. Diabetes 10:432, 1961.

While not common, severe insulin deficiency can cause hyperlipemia:

91) Kessler, J. I. Effect of diabetes and insulin on the activity of myocardial and adipose tissue lipoprotein lipase of rats. J. Clin. Invest. 42:362, 1963.

Diabetes decreases and insulin restores adipose tissue LPL in rats (myocardial LPL responds in opposite manner).

92) Brown, D. F. Triglyceride metabolism in the alloxan-diabetic rat. Diabetes 16:90, 1967.

Insulin deficiency decreases triglyceride uptake by adipose tissue due to depression in lipoprotein lipase.

93) Bagdade, J. D., Porte, D. and Bierman, E. L. Diabetic lipemia. A form of acquired fat-induced lipemia. N. Eng. J. Med. 276:427, 1967.

Consistent with decrease in LPL insulin deficiency (diabetes) in man results in chylomicra accumulation, i.e. "acquired fat-induced lipemia".

PANCREATITIS AND HYPERLIPEMIA

Alcoholic pancreatitis rarely is accomplished by hyperlipemia:

94) Greenberger, N. J., et al. Pancreatitis and hyperlipemia. Medicine 45:161, 1966.

Only 3 of 25 patients with pancreatitis developed hyperlipemia and in each of the 3, hyperlipemia was probably primary.

If pancreatitis is severe enough to cause insulin deficiency, hyperlipemia may result:

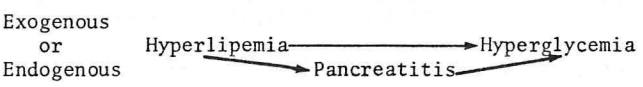
95) Bagdade, J. D. Diabetic lipaemia complicating acute pancreatitis. Lancet, Nov. 15:1041, 1969.

Alcoholic pancreatitis causes transient hyperglycemia and hyperlipemia.

The common situation involves primary hyperlipemia (fat-induced or endogenous causing pancreatitis with or without hyperglycemia:

96) Klatskin, G. and Gordon, M. Relation between relapsing pancreatitis and essential hyperlipemia. Amer. J. Med. 12:3, 1952.

Emphasizes that hyperlipemia can cause recurrent pancreatitis.



Acute alcoholism can itself cause transient hyperlipemia with or without pancreatitis:

97) Albrink, M. J. and Klatskin, G. Lactescence of serum following episodes of alcoholism and its probable relationship to acute pancreatitis. Amer. J. Med. 23:26, 1957.

Five patients with acute alcholism and hyperlipemia.

98) Zieve, L. Jaundice, hyperlipemia and hemalytic anemia. A heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. Ann. Int. Med. 48:471, 1958.

Acute alcholic intake plus cirrhosis led to syndrome in ten patients.

99) Jones, D. P., et al. Effects of ethanol on plasma lipids in man. J. Lab. Clin. Med. 62:675, 1963.

Alcohol will frequently cause elevation in triglycerides in normal people.

RENAL HYPERLIPEMIA

100) Baxter, J. H., Goodman, H. C. and Havel, R. J. Serum lipid and lipoprotein alterations in nephrosis. J. Clin. Invest. 39:455, 1960.

Still the best study of lipids in the nephrotic syndrome.

101) Schreiner, G. F. The nephrotic syndrome. In The Kidney. Strauss and Welt, eds. Little-Brown, p. 335.

A good reveiw of the hyperlipemia of nephrosis with 1° data showing that elevated triglyceride levels are related to low albumen concentrations. Mild hypoalbuminuria may lead to hypercholesterolemia without hyperlipemia, i.e. clear plasma.

102) Chopra, J. S. and Mallick, N. P. Hyperlipoproteinaemias in nephrotic syndrome. Lancet 1:317, 1971.

The hypertriglyceridemia of nephrosis is primarily of the endogenous type.

103) Berlyne, G. M. and Mallick, N. P. Ischaemic heart-disease as a complication of nephrotic syndrome. Lancet 2:399, 1969.

The hyperlipemia of nephrosis if chronic is not benign, can cause premature atherosclerosis, and should be treated probably with Atromid-S. Four of fifteen patients with hyperlipemia (average duration 3.5 years) secondary to nephrosis had myocardial infarctions, a fifth patient developed angina on effort. MI was the second most common cause of death in nephrotic patients.

104) Bagdade, J. D., Porte, D., Jr., and Bierman, E. L. Hypertriglyceridemia: a metabolic consequence of chronic renal failure. New Eng. J. Med. 279:181, 1968.

Renal failure results in elevated triglyceride levels even without albuminuria. Cause is ? increased hepatic synthesis and decreased lipoprotein lipase.

ORAL CONTRACEPTIVES

105) Brody, S., et al. The effects of some ovulation inhibitors on the different plasma lipid fractions. Acta Med. Scand. 183:1, 1968.

The most careful evaluation of contraceptive pills on plasma lipids. Estrogens raise and progesterones lower triglycerides.

106) Wynn, V. Fasting serum triglyceride, cholesterol, and lipoprotein levels during oral-contraceptive therapy. Lancet, Oct. 11:756, 1969.

Oral contraceptives cause a slight rise in triglyceride (only 4 of 164 women had elevations over 200 mg%). Cholesterol is even less affected.

107) Hazzard, W. R., et al. Studies on the mechanism of increased plasma triglyceride levels induced by oral contraceptives. New Eng. J. Med. 280:471, 1969.

Confirms the slight rise in triglyceride produced by contraceptive pills, and demonstrates a decrease in post heparin LPL activity following contraceptive pill treatment.

GLYCOGEN STORAGE DISEASE

108) Jakovcic, S., Khachadurian, A., and Hsia, D. The hyperlipidemia in glycogen storage disease. J. Lab. Clin. Med. 68:769, 1966.

The mechanism of hyperlipemia in glycogen storage disease remains poorly understood. Correcting the hypoglycemia does not correct the hyperlipemia.

EMOTIONAL STRESS AND TRIGLYCERIDES

109) Taggart, P. and Carruthers, M. Endogenous hyperlipidaemia induced by emotional stress of race driving. Lancet 1:363, 1971.

Triglyceride levels can increase as much as ten-fold approximately one hour after completion of international auto competition.

110) Bellet, S., Roman, L. and Kostis, J. The effect of automobile driving on catecholamine and adrenocortical excretion. J. Cardiology 24:365, 1969.

Driving to work in city (Philadelphia) traffic causes almost a doubling ($P < 0.01$) in catecholamine levels.