PARKLAND MEMORIAL HOSPITAL

MEDICAL GRAND ROUNDS

October 1, 1964

ESSENTIAL HYPERLIPEMIA

CASE 1. Fat Induced Hyperlipemia. [redacted])

The patient is a 31 year old [redacted] woman who was admitted to [redacted] on [redacted]/63 with a chief complaint of severe parietal-occipital headaches of three weeks duration. These were throbbing in nature and were accompanied by stiffness of the neck and at times by projectile vomiting During the two weeks prior to admission the patient noted frequent dizziness, drowsiness, and at times bilateral scotoma. She volunteered the information that these symptoms were aggravated by eating pork chops or other fatty foods.

The patient gave a nine months history of having episodes of abdominal pain and vomiting especially after fatty meals.

The patient's family history indicated her father died of unknown causes at age 55; one brother had died in the early forties of myocardial infarction; seven sisters and three brothers were noted to be living and well. There was no past history of diabetes.

On examination the patient's blood pressure was 120/70. Temperature was 99.4°. Funduscopic examination revealed marked papilledema bilaterally. Both arteries and veins appeared to be white in color; a flame-shaped hemorrhage could be seen in the right fundus. Several eruptive xanthoma were noted on the left elbow. No hepatomegaly was detected and the remainder of the physical examination was normal.

On admission the patient's serum was noted to be grossly lipemic. A blood cholesterol obtained two days after admission was 1,269 mg.%. The blood triglyceride was 9,722 mg.% (normal 0-200 mg.%). The patient was placed on a regular diet but on [redacted]/63, because of the possibility that continuing papilledema was due to hyperlipemia, all oral food intake was stopped and she was maintained solely on I.V. glucose. Gross clearing of the lipemia was apparent by [redacted]/63; triglyceride concentration decreasing to 488 mg.% and cholesterol level decreasing to 716 mg.% This was accompanied by definite subjective improvement with decrease in the headaches. Despite the relative clearing of the plasma, the patient's papilledema, while decreasing, was still definitely present. For this reason on [redacted]/63 a pneumoencephalogram was performed; no abnormalties were noted. The patient was maintained on the 20-30 gram fat diet with continued subjective improvement and probable decrease in papilledema.

Heparin tolerance test performed on [redacted]/63 showed no clearing of lipemia following 50 mg. of heparin I.V. The patient's PBI was 4.7 µg.%. An examination of visual fields showed an enlarged blind spot compatible with the 4+ papilledema observed during the examination. Fasting cholesterols were obtained on three of the patient's sisters and her daughter and were found to be within normal limits.

The patient was discharged on a low fat diet, D-Thyroxine, (4 mg./day), and Nicalex (3 g./day). She took these drugs only intermittently but when seen on [redacted]/63, serum was noted to be crystal clear and the cholesterol had decreased to 205 mg.%. On funduscopic the discs, however, were noted still to be flat, with questionable haziness of the disc borders. The patient remained on her low fat diet reasonably well, but took her medications only erratically. Her blood cholesterol was found to be 215 mg.% on [redacted]/63; 168 mg.% on [redacted]/63. On [redacted]/63, after stopping all medications, her cholesterol level was 175 mg.%, and from then until [redacted]/64, her cholesterol level was maintained at approximately 200 mg.%.

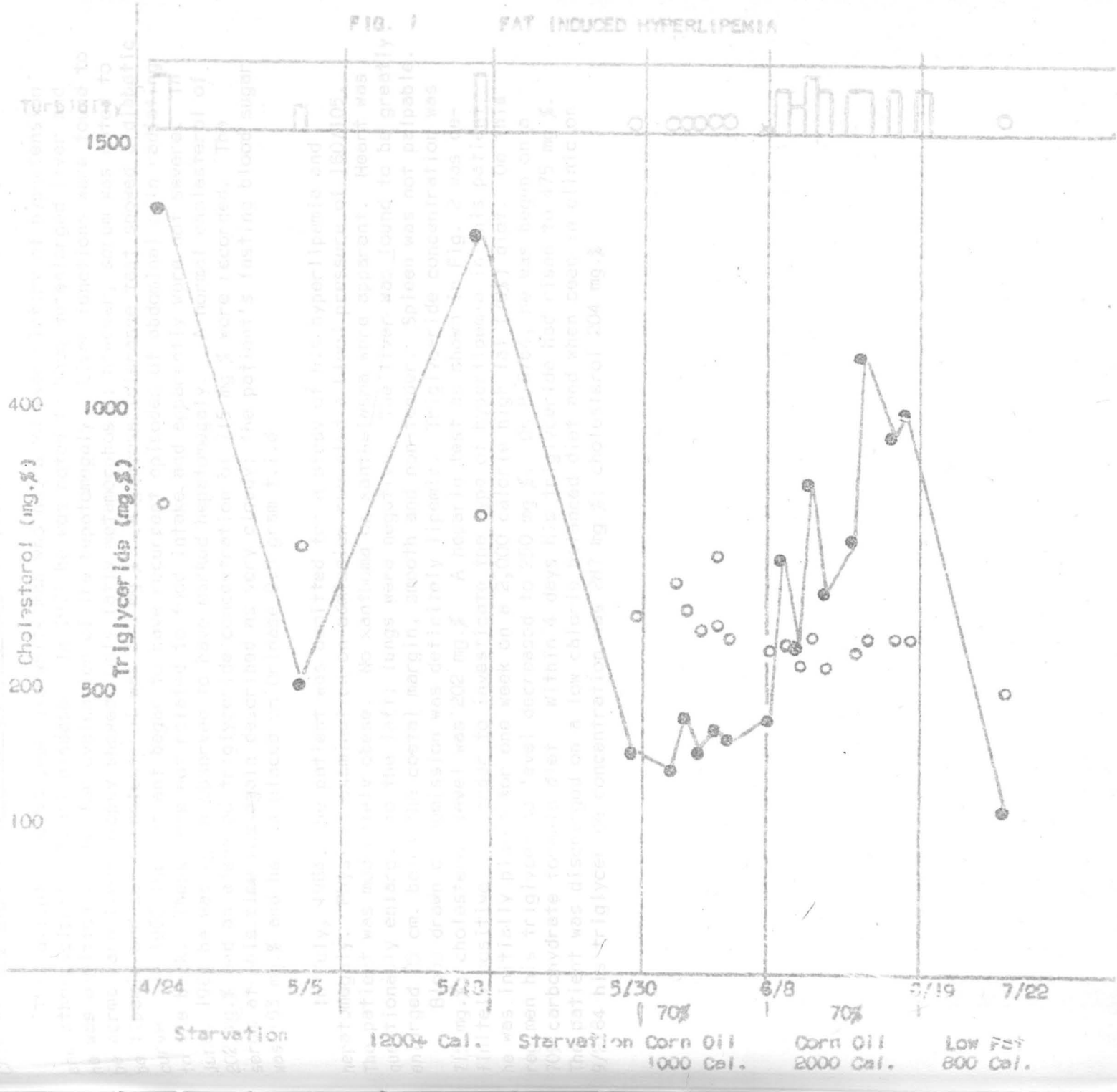
CASE 2. Fat Induced Hyperlipemia. ([redacted])

The patient is a 60 year old [redacted] man who for approximately 4 years has had known mild hyperglycemia readily controlled on Orinase. The patient had suffered from marked obesity for many years and was admitted to [redacted] on [redacted]/64 for treatment with a starvation diet.

On admission it was noted that his blood was lipemic and lipid analysis, as shown in Fig. 1, confirmed this impression, his cholesterol being 336 mg.% and his triglyceride concentration 1,406 mg.%. A heparin test showed no clearing of the plasma at one, two, or three hours after a 50 mg. dose of heparin. After 13 days of complete starvation, the patient's triglyceride concentration had decreased to 529 mg.% and the cholesterol level to 308 mg.%. However, following one week of a 1,200 calorie diet (taken while on pass) his triglyceride level had returned to its previous elevated state of 1,378 mg.%.

In an attempt to determine whether the patient's hyperlipemia was fat-induced, he was first placed on a 70% fat, 1,000 calorie diet for one week and then on a 70% fat, 2,000 calorie diet for the following 11 days. On the latter regimen, which according to Ahrens should cause a decrease in triglyceride level in a carbohydrate-induced hyperlipemic, the patient's triglyceride concentration rose to a high of 1121 mg.%. Clear-cut lipemia was apparent. On discharge the patient was placed on a 800 calorie, moderately low fat diet. His triglyceride level when last seen on [redacted]/64 was only slightly above normal at 300 mg.%, cholesterol was normal at 203 mg.%, and the plasma was completely clear.

FIG. 1 FAT INDUCED HYPERLIPEMIA



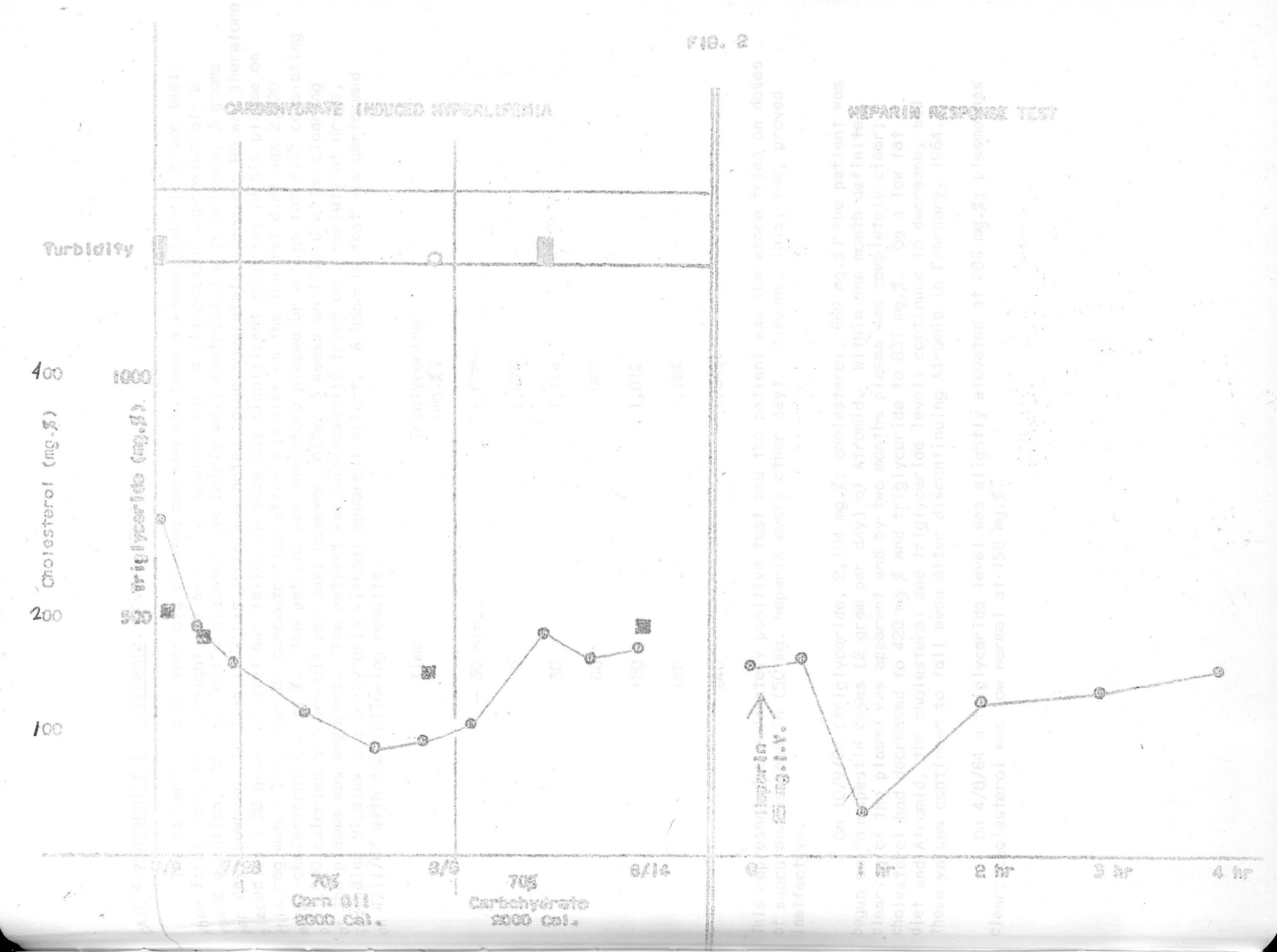
CASE 3. Carbohydrate Induced Hyperlipemia. [redacted])

The patient is a 53 year old [redacted] man who has a 20 year history of hypertension and atherosclerotic heart disease. In 1961 he was noted to have an enlarged liver and he was admitted to [redacted] for evaluation of the hepatomegaly Liver functions were found to be normal and liver biopsy showed only fatty metamorphosis; however, serum was noted to be lipemic and serum cholesterol was 310 mg.%. A glucose tolerance test showed a diabetic curve In 1962 the patient began to have recurrent episodes of abdominal pain radiating to the back. These were not related to food intake and apparently were not severe. In [redacted], 1964 he was again observed to have marked hepatomegaly. A normal cholesterol of 202 mg.% and an elevated triglyceride concentration of 715 mg % were recorded. The serum at this time was again described as very cloudy; the patient's fasting blood sugar was 163 mg.% and he was placed on Orinase 0.5 gram t.i.d.

In [redacted], 1964, the patient was admitted for a study of his hyperlipemia and hepatomegaly. Physical examination on admission revealed a blood pressure of 160/105. The patient was moderately obese. No xanthoma or xanthelasma were apparent. Heart was questionably enlarged to the left; lungs were negative. The liver was found to be greatly enlarged 25 cm. below the costal margin, smooth and non-tender. Spleen was not palpable.

Blood drawn on admission was definitely lipemic. Triglyceride concentration was 715 mg.%; cholesterol level was 202 mg.% A heparin test as shown in Fig. 2 was definitely positive In order to investigate the type of hyperlipemia in this patient he was initially placed for one week on a 2,000 calorie high fat (70%) diet. On this regimen his triglyceride level decreased to 250 mg.%. On [redacted]/64, he was begun on a 70% carbohydrate formula diet Within 4 days his triglyceride had risen to 475 mg.%. The patient was discharged on a low calorie balanced diet and when seen in clinic on [redacted]/64 his triglyceride concentration was 287 mg.%; cholesterol 204 mg.%.

FIG. 2


CARBOHYDRATE INDUCED HYPERLIPEMIA
HEPARIN RESPONSE TEST
Turbidity
Cholesterol (mg.%)
Triglyceride (mg.%)
400
200
100
1000
500
7/8
7/28
8/6
8/14
70% Corn Oil 2000 Cal.
70% Carbohydrate 2000 Cal.
Heparin 50 U.S.P. I.V.
0
1 hr
2 hr
3 hr
4 hr

CASE 4.?Metabolic Hyperlipemia. [redacted]

The patient is a 57 year old [redacted] man who has been a known diabetic since 1961. When first seen, his eyesight was severely impaired due to glaucoma of approximately 2 years duration. The patient's diabetes was fairly well controlled with Orinase, 3 grams per day; however, in [redacted] 1962 his serum was noted to be moderately lipemic. He was therefore placed on a 30 gram fat diet but failed to show any significant clearing in his plasma on this regimen. Triglyceride concentration after 4 months on the low fat diet was 2,220 mg.%; cholesterol 602 mg.%. The patient was therefore placed on a high fat diet consisting of 1,000 calories of corn oil per day; however, after 3 weeks on this diet no clearing of the plasma was apparent. The patient was subsequently tried on a variety of drugs, including Nicalex and D-thyroxin without apparent effect. A heparin test was performed on [redacted]/63 with the following results:

Time	Triglyceride (mg.%)
- 30 min.	1,632
0	1,676
30	1,144
60	996
120	1,012
180	1,124
240	1,248.

This represented a moderately positive test and the patient was therefore tried on doses of subcutaneous heparin (50 mg. heparin every other day). However, this, too, proved ineffective.

On [redacted]/63 (triglyceride, 2,104 mg.%; cholesterol, 669 mg.%) the patient was begun on therapeutic doses (2 gram per day) of Atromid. Within one month definite clearing of the plasma was apparent and by two months plasma was completely clear; cholesterol had decreased to 422 mg % and triglyceride to 837 mg.%. On a low fat diet and Atromid, the cholesterol and triglyceride levels continued to decrease, and these values continued to fall even after discontinuing Atromid in [redacted], 1964.

On [redacted]/64 a triglyceride level was slightly elevated at 286 mg.%; plasma was clear; cholesterol was low normal at 158 mg.%.

FAT METABOLISM

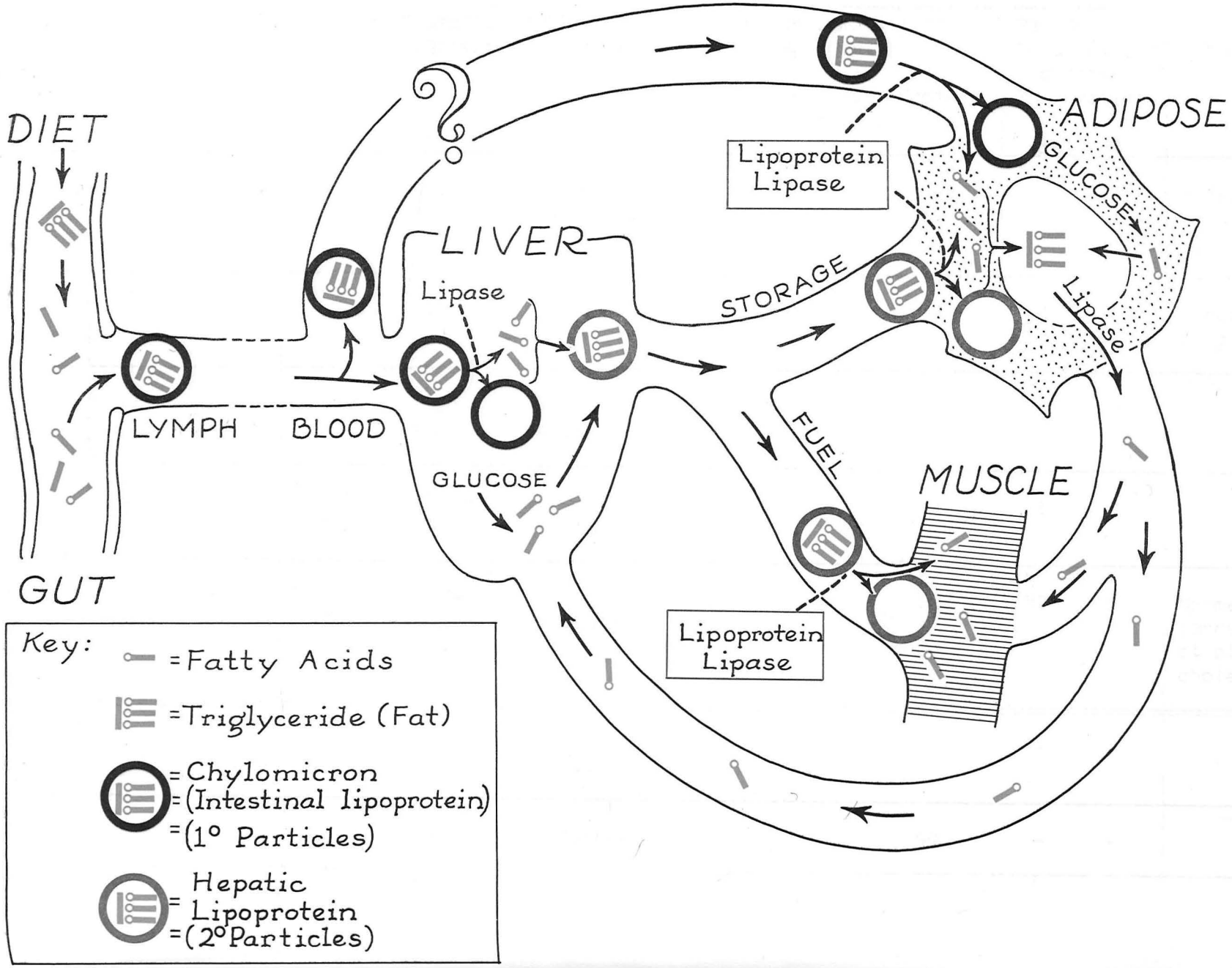


TABLE I

PLASMA LIPOPROTEINS

		Lipemia	Density	Flotation (Gofman)	Electro-Phoresis	Chemical Composition (Per Cent)			Per Cent of Total Plasma Cholesterol in Fraction		Comment
						Triglyc-eride	Choles-terol	Protein	♂	♀	
"Primary" Fat Particles		+	<1.006	S_f 1 000-40,000	α_2 (with some β globulin	90	6	1	4	4	Intestinal origin
"Secondary" Fat Particles		+	<1.006	S_f 400 - 1,000	β globulin	90	6	1	4	4	Hepatic origin
Very Low Density Lipoproteins	"β-lipoprotein"	-	<1.006	S_f 20 - 400	β globulin	56	23	7	7	7	
Low Density Lipoproteins	"β-lipoprotein"	-	1.006-1.019	S_f 12-20	β globulin	30	43	11	8	8	
Low Density Lipoproteins		-	1.019-1.063	S_f 0-12	β globulin	10	58	20	57	51	Normally carry most of plasma cholesterol
High Density Lipoproteins	"α-lipoprotein"	-	1.063-1.21	-	α globulin	15	35	45	24	30	
Free Fatty Acids		-		-	albumen			99	-	-	

TABLE II

CLASSIFICATION OF ESSENTIAL HYPERLIPEMIA

	Type	Plasma Lipids	Plasma Appearance	Defect	Heparin Test	Xanthoma	Clinical Characteristics	Treatment
1	"Fat Induced"	High triglyceride (primary particles) cholesterol may be normal or high	Cream, separates on standing at 0°C	Lipoprotein lipase defect	No response	Eruptive and ?tuberous NO xanthelasma	Abdominal crisis hepatosplenomegaly	Low fat
				Heparin defect (probably very rare)	Respond	"	"	Low fat + heparin
2	"Carbohydrate Induced"	High cholesterol predominates and only moderate elevation of triglyceride (secondary particles)	Skimmed milk, Does not separate at 0°C	Overproduction of secondary particles by liver on carbohydrate diet	Respond	Eruptive, tuberous tendonous and xanthelasma	Atherosclerosis	High unsaturated fat
3	Primary hypercholesterolemia with hypertriglyceridemia							
4	"Metabolic"	Triglyceride and cholesterol may be proportionally high	Probably cream	?Hormonal	±	Probably all	?	1) Probably low fat, 2) Atromid? 3) Nicalex
	Primary hypercholesterolemia	High cholesterol only; triglyceride normal	Clear	Unknown	-	Tuberous, tendonous xanthelasma. No eruptive	Atherosclerosis	High polyunsaturated fat

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5% fat-high carbohydrate diets will raise triglyceride level in normal men; triglyceride concentrations will decrease on 20% fat diet and are lowest at a "normal" 40% fat level.

58. Antonis, A. and Bersohn, I. The Influence of Diet on Serum Triglycerides. Lancet 1:3, 1961
Paper makes three important points: 1) low fat diets cause marked rise in triglyceride level in normal men; however 2) triglycerides subsequently return to normal but only after 30 weeks on diet. 3) Unsaturated fat in a normal (40% fat diet) causes lowering, and saturated fat (butter) raises triglyceride levels in normal men.

Inheritance and Incidence of Hyperlipemia

59. Hirschhorn, K. Incidence of Familial Hyperlipemia. Science 129:716, 1959.
Amongst Swedish students the incidence of hyperlipemia is about 3%.
See also Ref. 65.

60. Bialkin, G., Zucker, S., Sklarin, B. S., Hirschhorn, K., and Davidsen, M. A Genetic and Metabolic Study of a Family with Hyperlipemia. Ped. 29:566, 1962.
Describe 3 siblings and half sister with hyperlipemia unresponsive to heparin but decreasing on a low fat diet. Conclude that disease is inherited as an incomplete dominant (parents had normal lipid levels), with homozygous more severe than heterozygous in children.

Atherosclerosis in Essential Hyperlipemia

61. Soffer, A. and Murray, M Prolonged Observation of the Cardiovascular Status in Essential Hyperlipemia. Circulation 10:255, 1954.
Indicate that hyperlipemia can be accompanied by severe atherosclerosis, but all except one of seven patients had primarily cholesterol elevation. Good description of heparin test.

62. Martt, J. M., Connor, W. E. Idiopathic Hyperlipemia Associated with Coronary Atherosclerosis Arch Int.Med. 97:492, 1956
Describe a patient with probable essential hyperlipemia, myocardial infarction and death at age 39.

63. Adlersberg, D., and Wang, C Syndrome of Idiopathic Hyperlipemia, Mild Diabetes and Severe Vascular Damage Diab. 4:210, 1955.
Hyperlipemia is described in 5 patients with carbohydrate abnormalities and vascular disease. Low fat (and low calorie) diets lowered lipids in each.

Relation of Triglycerides to Atherosclerosis

64. Nicols, A. V., Lindgren, F. T. and Gofman, J. W. Estimation of Atherogenic Index and Lipoprotein Distribution in Men. Geriatrics 12:130, 1957.
Total lipids, i.e. primarily triglycerides, are well correlated with "atherogenecity".

65. Albrink, M. J., Man, E. B. and Peters, J. P. The Relation of Neutral Fat to Lactescence of Serum. J. Clin. Invest. 34:147, 1955.
Lactescence of serum occurs invariably at triglyceride levels of 550 mg.%.

66. Albrink, M. J., Meigs, J. W. and Man, E. B. Serum Lipids, Hypertension and Coronary Artery Disease. Am. J. Med. 31:4, 1961.
Presents argument that triglycerides are more important than cholesterol in development of atherosclerosis. If upper limit of normal is 150 mg.%, 25% of men over 40 have hypertriglyceridemia.

67. Rutstein, D. D., Castelli, W. P., Sullivan, J. C., Newell, J.M. and Nickerson, R.J. Effect of Fat and Carbohydrate Ingestion in Human B ings on Serum Lipids and Intracellular Lipid Deposition in Tissue Culture. N. Eng. J. Med. 271:1, 1964.
Deposition of blood lipid in tissue culture is better related to triglyceride concentration than to cholesterol level.
See also Ref. 13.

Drug Therapy of Hyperlipemia

Nicalex

68. See Boyle, Ref. 43.

69. See Kuo, et al. Ref. 44.

Atromid

70. Hellerman, L., Zumoff, B. Kessler, G., Kara, E., Rubin, I. L. and Rosenfeld, R.S. Reduction of Cholesterol and Lipids in Man by Ethyl p-Chlorophenoxyisobutyrate. Ann. Int. Med. 59:477, 1963.
Atromid (ethyl chlorophenoxyisobutyrate) ("CPIB") appears to lower triglyceride levels specifically. Effect greater in women than in men.

71. Howard, R. P., Alaupovic, P., Brusco, O. J. and Furman, R. H. Effects of CPIB Alone and with Androsterone (Atromid) on Serum Lipids, Lipoproteins and Related Metabolic Parameters in Normal and Hyperlipedemic Subjects. J. Athero. Research 3:482, 1963.
CPIB is particularly effective in reducing low density lipoproteins in hyperlipemic patients.

Heparin

72. Furman, R. H., Howard, R. P. and Alaupovic, P. Effect of Chronic Heparin Administration on Serum Lipids, Lipoproteins, Nitrogen and Electrolyte Balance in Normal and Heparin-Responsive and Heparin-Unresponsive Hyperglyceridemic Subjects. Met. 11:879, 1962.
Chronic heparin administration will lower triglyceride and cholesterol in sensitive subjects.

Hyperlipemia in Diabetes

73. Campbell, J. Hyperlipidemia with Ketoacidosis. Metabolism 11:762, 1962.
A complete review of the lipid derangements of diabetes with discussion of the causes of hypertriglyceridemia in the uncontrolled diabetic.

74. Hamwi, G., et al. Hyperlipemia in Uncontrolled Diabetes. Metabolism 11:850, 1962.
Carefully documents the hyperlipedemia of diabetics in poor control. A minor elevation of triglyceride however may persist even with good control.

75. Bierman, E. L. and Hamlin, J. T., III. The Hyperlipemic Effect of a Low Fat, High Carbohydrate Diet in Diabetic Subjects. Diabetes 10:432, 1961.
Diabetics placed on a fat-free diet respond, as do normal patients, with an increase in serum triblycerides.

76. New, M. I., Roberts, T. N., Bierman, E. L., Reader, G. G. The Significance of Blood Lipid Alterations in Diabetes Mellitus. Diabetes 12:208, 1963.
Until age 50 there is probably no significant difference between triglyceride levels in normal and well controlled diabetic patients. But see Ref. 74 and 77.

77. Albrink, M. J. Diet, Diabetes and Serum Lipids. Diabetes 13:425, 1964.
Summarizes evidence that elevated serum triglyceride is related to atherosclerotic complications of diabetes.

78. Buckle, R. M. Mobilization of Free Fatty Acids from Adipose Tissue from Normal and Diabetic Subjects. Diabetes 12:133, 1963.
The last of several papers clearly demonstrating that uncontrolled diabetic animals release more free fatty acids from adipose tissue than do normal animals.

79. Schnatz, J. D. and Williams, R. H. The Effect of Acute Insulin Deficiency in the Rat on Adipose Tissue Lipolytic Activity and Plasma Lipids. Diabetes 12:174, 1963.
Clearly shows that insulin deprivation causes a prompt decrease in adipose tissue lipoprotein lipase, and serum triglyce ide level rises.

Hyperlipemia in Nephrosis

The following two reviews critically summarize the extensive literature in this area and conclude that hypoalbuminemia probably plays a major role in the causation of the hypertriglyceridemia of nephrosis.

80. Baxter, J. H. Hyperlipoproteinemia in Nephrosis. Arch. Int. Med. 109: 742, 1962.

81. Studies of Lipid Metabolism in Nephrosis. Nutr. Rev. 20:297, 1962.

Alcohol and Hyperlipemia

82. Amatuzio, D. S. and Hay, L. J. Dietary Control of Essential Hyperlipemia. Effects of Dairy Foods, Phospholipid, Coconut Oil and Alcohol. Arch. Int. Med. 102:173, 1958.
Alcohol alone will increase triglycerides in certain hyperlipemic patients. Elimination of alcohol and dairy products decreased lipids to normal in 9/12 patients.

83. Losowsky, M. S., Jones, D. P., Davidson, C. S. and Lieber, C. S. Studies of Alcoholic Hyperlipemia and Its Mechanism. Amer. J. Med. 35:794, 1963.
Lipemia is described in 8 patients with acute alcoholism. Alcohol given with adequate diet can cause lipemia in susceptable subjects. Lipoprotein lipase was below normal in the lipemic patients.

84. Jones, D. P., Losowsky, M. S., Davidson, C. S. and Lieber, C. S. Effects of Ethanol on Plasma Lipids in Man. J. Lab. & Clin. Med. 62:675, 1963.
Alcohol will cause increase in triglycerides within 6 hours.

Zieve's Syndrome

85. Zieve, L. Jaundice, Hyperlipemia and Hemolytic Anemia: A Heretofore Unrecognized Syndrome Associated with Alcoholic Fatty Liver and Cirrhosis. Ann. Int. Med. 48:471, 1958.
Describes the above triad in 20 patients. Actually 10 of 20 had hyperlipemia documented.

86. Kessel, L. Acute Transient Hyperlipemia Due to Hepatopancreatic Damage in Chronic Alcoholics (Zieve's Snydrome). Am. J. Med. 32:747, 1962.
Six more cases of Zieve's Syndrome described. Hyperlipemia is the most prominent symptom.