Chylomicronemia Syndrome in Diabetes Mellitus

ALAN CHAIT, H. THOMAS ROBERTSON, AND JOHN D. BRUNZELL

Lipemic plasma with marked elevations of plasma triglyceride levels (3221 ± 1590 mg/dl) and fasting chylomicronemia was observed in nine patients with uncontrolled non-insulin-dependent diabetes mellitus. Every case had hypertriglyceridemic relatives, suggesting that the very high triglyceride values seen resulted from the coexistence of diabetes with a familial form of hypertriglyceridemia. A number of clinical and biochemical features observed in the diabetic patients and also in a group of nondiabetic controls with comparable degrees of hypertriglyceridemia suggests that these manifestations are related to high plasma triglyceride levels rather than to the diabetes per se. Chronic abdominal pain, mental confusion, and memory loss improved with lipid-lowering therapy and clearing the plasma of chylomicrons. Pulmonary function tests, red cell 2,3-diphosphoglycerate, and hemoglobin oxygen affinity were normal; the mild hypoxemia observed is believed to be an artifact. It is suggested that a syndrome due to chylomicronemia can occur in uncontrolled non-insulin-dependent diabetic patients, who in addition have a familial form of hypertriglyceridemia. To prevent manifestations of this syndrome in these patients, specific lipid-lowering therapy may be required in addition to control of their diabetes. DIABETES CARE 4: 343–348, MAY–JUNE 1981.

Chylomicrons, the large triglyceride-rich lipoproteins that transport dietary fat through plasma, are ordinarily rapidly cleared from plasma by the action of lipoprotein lipase.[1] The activity of this enzyme is reduced in uncontrolled diabetes mellitus[2,3] and is essentially zero in primary lipoprotein lipase deficiency.[4,5] In primary lipoprotein lipase deficiency, chylomicrons accumulate in plasma even in the fasting state and result in very high plasma triglyceride levels and a lipemic-appearing plasma. However, untreated diabetes alone usually results in mild to moderate rather than marked hypertriglyceridemia. Since the lipoprotein lipase-related triglyceride-removal system is saturable,[6] the coexistence of other causes of hypertriglyceridemia in addition to untreated diabetes can lead to profound hypertriglyceridemia and chylomicronemia.[7]

A number of clinical and biochemical manifestations have been associated with chylomicronemia including abdominal pain,[8] eruptive xanthomata,[8] pancreatitis,[7,9,10] hepatosplenomegaly,[8] lipemia retinalis,[8] hypoxemia,[11,12] abnormal hemoglobin oxygen affinity,[13] decreased pulmonary diffusing capacity,[14,15] and psychological changes.[16,17] It is not clear whether these manifestations are related to the chylomicronemia per se or whether they are related to associated conditions such as diabetes mellitus.

This article describes the clinical features in a group of non-insulin-dependent diabetic patients referred for evaluation because of the finding of lipemic plasma, and compares them with clinical features in nondiabetic subjects with comparable degrees of hypertriglyceridemia. Many manifestations of this syndrome improved with treatment of the chylomicronemia irrespective of its cause, suggesting that these clinical features were related to the chylomicronemia rather than the diabetes. However, diabetes appears to be important in the etiology of the chylomicronemia seen, by interacting with familial forms of hypertriglyceridemia.

PATIENTS AND METHODS

Patient selection. Nine of 10 consecutive patients referred to us because of uncontrolled nonketotic diabetes mellitus (diagnosed on the basis of repeated fasting plasma glucose levels above 140 mg/dl) and "milky" plasma (marked lipemia with chylomicrons present in blood obtained after a 12–14-h fast) were included in the study (Table 1). The tenth was

TABLE 1
Patient populations

Patient no.	Age/Sex	Plasma triglyceride concentration		Initial fasting* plasma glucose	Etiologic factors other than diabetes
		Initial	After treatment		
A. Diabetic					
1	51/M	3680	664	289	Familial hypertriglyceridemia
2	50/M	2500	158	309	Familial—precise diagnosis uncertain
3	49/M	2000	265	272	Familial hypertriglyceridemia
4	33/M	6600	640	342	Familial combined hyperlipidemia
5	80/F	1855	540	140	Familial—precise diagnosis uncertain
6	70/M	2340	975	310	Familial hypertriglyceridemia
7	53/F	2580	*	130	Broad-beta disease
8	65/F	2480	194	203	Estrogens plus familial—precise diagnosis uncertain
9	50/M	4950	565	249	Familial hypertriglyceridemia
B. Nondiabetic					
1	29/M	1630	196	86	Primary lipoprotein lipase deficiency
2	21/M	960	208	94	Primary lipoprotein lipase deficiency
3	30/M	6275	*	89	Familial on both sides of family
4	41/M	6050	*	94	Primary lipoprotein lipase deficiency

* Measured on the day of admission or the following day.
† Not restudied after treatment.

excluded because she presented with severe, acute pancreatitis and was too ill for adequate evaluation while chylomicronemic. All nine patients evaluated had fasting plasma triglyceride levels in excess of 1850 mg/dl; above this concentration we invariably find chylomicrons in plasma obtained 12–14 h after the last meal.

Four of the nine patients were known to be diabetic previously (duration of diabetes ranged from 1 to 7 yr). Of these, three were previously known to be hyperlipidemic (duration ranged from <1 to 7 yr) and were admitted on the present occasion with worsening of their diabetic control. Two had been taking chlorpropamide, while two received no specific therapy. The remaining five diabetic subjects, two of whom were previously known to have a familial form of hypertriglyceridemia, had their diabetes diagnosed at the time of the present admission.

Four nondiabetic controls with fasting chylomicronemia, in whom no secondary cause of hypertriglyceridemia was found, were studied for comparison. Primary lipoprotein lipase deficiency was diagnosed in three subjects by the absence of this enzyme from biopsies of subcutaneous adipose tissue.[5] The remaining case was found to have a familial form of hypertriglyceridemia in both of his parents (Table 1).

Study protocol. The patients were admitted to the Clinical Research Center of the University Hospital, Seattle. Pulmonary function and psychometric evaluation tests were performed within 1 day of admission. Treatment was then instituted to rapidly lower the elevated plasma triglyceride levels and to clear the plasma of chylomicrons. This was done to determine which clinical and biochemical features improved with resolution of the hypertriglyceridemia. The precise therapeutic regimen chosen varied according to clinical indications. All patients, diabetic and nondiabetic, were started on a 600-calorie, fat-free formula diet to rapidly lower plasma triglyceride levels. The diabetes in six patients was treated with chlorpropamide 250–500 mg/day. No additional therapy for diabetes was needed after weight loss in two further diabetic patients and discontinuation of estrogen in a third. To facilitate rapid resolution of the chylomicronemia, all the diabetic patients other than the one taking estrogen received clofibrate (Atromid-S) 1 g b.i.d. in addition. The one control patient with a familial form of hypertriglyceridemia in both parents also received clofibrate. After a period of 10–21 days, by which time plasma triglyceride levels had fallen substantially (mean posttreatment value = 441 ± 276 mg/dl) and fasting chylomicronemia was no longer present (Table 1), these tests were repeated in eight diabetic and two nondiabetic subjects. Three subjects (diabetic no. 7 and nondiabetic nos. 3 and 4) were only studied initially and were not reevaluated.

Methods. Plasma triglyceride levels were measured on an AAII autoanalyzer using standard Lipid Research Clinic techniques.[18] Chylomicronemia was confirmed in all cases by the appearance of fasting plasma refrigerated for 12–16 h at 4°C[19] or by flotation in 3% polyvinylpyrrolidone.[20] Secondary causes of hypertriglyceridemia were sought by appropriate testing,[21,22] and family studies to evaluate the possibility of a genetic component to the hypertriglyceridemia were performed as previously described.[23] The diagnosis of primary lipoprotein lipase deficiency was made by the essential absence of enzyme activity in adipose tissue biopsies using methods previously described.[5]

Memory was assessed using the Wechsler Memory Test and objective psychiatric evaluation was performed using the Minnesota Multiphasic Personality Inventory (MMPI).

Static pulmonary function tests included spirometry and single breath diffusing capacity (DL_{COSB}). "Arterialized" blood gases were measured with a Radiometer BMS-3 system using blood obtained from earlobe puncture.[24] Hemoglobin affinity for oxygen[25] and red cell 2,3-diphosphoglycerate (2,3-DPG)[26] also were determined.

Statistics. Values are shown as mean ± standard deviation. Variables measured before and after lowering of plasma triglyceride levels were compared using the paired Student's *t* test or Wilcoxon's test where variances were nonhomogenous.

RESULTS

Etiology of the massive hypertriglyceridemia (chylomicronemia). In all nine diabetic subjects, another potential cause of the hypertriglyceridemia apart from uncontrolled diabetes was found. On the basis of family studies,[23] monogenic familial hypertriglyceridemia was subsequently diagnosed in four subjects and familial combined hyperlipidemia was found in one. One patient, with well-documented broad-beta disease, presented with plasma triglyceride levels much higher than her usual; uncontrolled diabetes which had not been present previously was found. In the remaining three diabetic patients, hyperlipidemic relatives were found by family study, thus indicating a familial lipid disorder. However, in these families too few relatives were available for study to allow a definitive genetic diagnosis to be established.[23]

Clinical features (Table 2). Abdominal pain was the most frequent presenting feature, occurring in 7 of the 9 diabetic patients (78%) and in all 4 nondiabetic chylomicronemic subjects. In all diabetic and in two nondiabetic subjects, the pain was chronic and did not resemble that of acute pancreatitis. The pain tended to be a midepigastric ache and bore no relationship to meals or bowel movements. The most characteristic feature was that it radiated through to the back. The pain had been present for several weeks to several months before admission. In all cases the pain had disappeared by the time of reevaluation when triglyceride levels had been lowered (500 ± 279 mg/dl versus 3221 ± 1590 untreated; $P < 0.001$; Table 1). Eruptive xanthomata occurred in 5 of 9 diabetic subjects (56%) and in all the nondiabetic ones. Lipemia retinalis was detected in only three patients, one diabetic, one with primary lipoprotein lipase deficiency, and in the patient with a familial form of hypertriglyceridemia on both sides of his family. Splenomegaly was present only in one subject with primary lipoprotein deficiency; hepatomegaly occurred in 11 of 13 subjects (8 diabetic, 3 nondiabetic).

Specific questioning elicited memory loss, especially for recent events in all the diabetic and in two nondiabetic subjects. Some patients also complained of the inability to think clearly, with difficulty in problem solving. None had any known organic cause of mental disturbance other than hypertriglyceridemia. The recent onset of central facial flushing with minimal alcohol intake was noted in two diabetic subjects (one of whom was taking chlorpropamide at the time) and in one nondiabetic subject. Symptoms of uncontrolled diabetes mellitus including weight loss, malaise, polyuria, and polydypsia of several weeks to months duration were among the chief complaints in 8 of the 9 diabetic subjects.

Pulmonary function tests (Table 3). FEV_1 and vital capacity were within normal limits in 11 of 12 patients (Table 3) and did not change with lowering of plasma triglyceride levels. Likewise, measurements of single breath diffusing capacity (DL_{COSB}) were within normal limits (mean = 98 ± 26% of predicted in diabetic subjects; 101 ± 4% of predicted in nondiabetic subjects) and did not change with treatment. One diabetic patient (no. 6) had chronic obstructive pulmonary disease. Mild arterial hypoxemia manifesting as an in-

TABLE 2
Clinical features

Patient no.	Abdominal pain	Eruptive xanthomata	Lipemia retinalis	Memory loss	Flushing after minimal alcohol intake
A. Diabetic					
1	+	+	−	+	−
2	−	+	−	+	−
3	+	+	−	+	−
4	+	+	+	+	*
5	+	−	−	+	*
6	−	−	−	+	*
7	+	−	−	+	+
8	+	+	−	+	−
9	+	−	−	+	+
B. Nondiabetic					
1	+	+	+	+	−
2	+	+	−	−	+
3	+	+	−	+	−
4	+	+	+	−	−

* Teetotaller.

TABLE 3
Pulmonary function tests in chylomicronemic patients

Patient no.	FEV_1	VC (% of predicted*)	DL_{COSB}	$(A\text{-}a)DO_2$ (mm Hg)
A. Diabetic				
1	100	97	†	29
2	80	95	80	23
3	83	93	89	18
4	98	100	104	24
5	112	104	135	36
6	48	63	104	†
7	107	94	96	27
8	142	146	102	45
9	109	102	118	9
$\bar{x}$	98	99	104	26
SD	26	21	17	11
B. Nondiabetic				
1	102	114	108	15
2	104	104	87	15
3	97	104	89	27
$\bar{x}$	101	107	95	19
SD	4	6	12	7

* For age, sex, and ideal body weight.
† Not measured.
FEV_1 = forced expiratory volume in 1 s; VC = vital capacity; DL_{COSB} = diffusing capacity for carbon monoxide, single breath; $(A-a)DO_2$ = upright alveolar arterial oxygen difference.

creased alveolar arterial oxygen difference [$(A - a)DO_2$] was documented on admission and improved significantly (27 ± 12 to 16 ± 9 mm Hg; N = 7; $P < 0.01$) after treatment. Diabetic and nondiabetic subjects responded similarly. P_{50} values (27.7 ± 1.0 mm Hg) were within normal limits (normal = 25.6–28.4) in all cases studied. Values for 2,3-DPG were also normal (4.8 ± 1.0 μg/dl packed red cells; N = 7; normal = 4–5). No differences between P_{50} and 2,3-DPG values were detected between diabetic and nondiabetic subjects.

Psychometric testing. Compared with baseline values, memory testing (Wechsler Memory Scale) improved by $10 \pm 3\%$ ($P < 0.05$) in 6 diabetic and 2 nondiabetic subjects with lowering of plasma triglyceride levels. The initial MMPI demonstrated psychiatric disturbances in 7 of 8 patients tested (6 diabetic, 2 nondiabetic; Table 4). These included depression (7 of 8), confusion (5 of 8), and disturbance of logical thought processes (5 of 8). Of the 8 patients retested after 10–21 days, logical thought processes, especially those related to visual functions, and confusion improved in 4 of 5, although measures of depression remained unchanged in 4 of 7. In the remaining three cases, the depressive element showed marginal improvement.

TABLE 4
Effect of lowering of plasma triglyceride levels on psychological abnormalities (detected by the MMPI)

MMPI abnormalities	Pretreatment	Plasma triglyceride: Better	Worse	No change
Depression	7/8	3/7	0	4/7
Confusion	5/8	4/5	0	1/5
Impaired logical thought processes	5/8	4/5	0	1/5

DISCUSSION

The main purpose of the study was to determine which clinical and laboratory features might be related to the lipemia per se rather than to the uncontrolled diabetes. Therefore, (1) a nondiabetic control group with chylomicronemia was selected that comprised three patients with primary lipoprotein lipase deficiency, and one with a familial form of hypertriglyceridemia in both sides of his family, and (2) studies were repeated after therapy aimed at resulting in a rapid resolution of the hyperlipidemia. Certain clinical manifestations occurred commonly with no consistent differences apparent between diabetic and nondiabetic groups. The most frequent complaint was that of abdominal pain. The association between hypertriglyceridemia and acute pancreatitis has been well documented previously.[7,9,10] A causal relationship between the chylomicronemia and pancreatitis is suggested by the observation that recurrent pancreatitis seen in association with lipemic plasma can be prevented by a dietary and drug regimen aimed at eliminating fasting chylomicronemia.[7] However, a more chronic type of abdominal pain often confused with such conditions as peptic ulceration, gall bladder disease, and the irritable bowel syndrome was seen in the present group of patients, whether diabetic or not. This pain, like the more acute variety, appeared to resolve rapidly with therapy that resulted in correction of the chylomicronemia.

The presence of marked hypertriglyceridemia with chylomicronemia should also be considered as a possible cause of confusional states, dementia,[16,17] or recent memory loss. In some cases, although memory function was initially in the normal to above normal range, improvement in memory was still observed. It is possible that this improvement could be attributed to hospitalization and improvement in diabetic control. However, the similar improvement noted in the nondiabetic controls, who were not acutely ill, suggests that the improvement in memory was indeed related to clearing of the chylomicronemia. The reason for the fairly frequent occurrence of psychiatric abnormalities in these patients is not clear. Certain psychiatric features such as depression are unlikely to be related to the chylomicronemia per se, since lowering of the plasma triglyceride concentration was associated with little improvement. However, confusion and disturbances of logical thought improved with triglyceride lowering, suggesting that these features and the memory loss are in fact related to the chylomicronemia.

In this study mild arterial hypoxemia [as evidenced by an

increased (A − a)DO_2] was a near universal finding in both diabetic subjects and controls. The finding of hypoxemia in association with hypertriglyceridemia in these cases is in keeping with early studies of Kuo and Whereat[11] and others.[12,13] Similar findings also have been reported following the infusion of fat emulsions.[15] Recent studies by our group suggest that the hypoxemia described in association with marked hypertriglyceridemia is an artifact secondary to an interaction between the lipemic plasma and the PO_2 electrode.[27] Furthermore, a second artifact due to light scattering by lipemic particles influences the spectrophotometric measurement of hemoglobin concentration and percent oxygen saturation,[27] which could explain some of the earlier findings in the literature.[12,13] The PO_2 electrode problem also could explain the observations of high hemoglobin oxygen affinities in patients with marked hypertriglyceridemia. When measured by a technique that minimizes the influence of the lipemic plasma on the PO_2 electrode, hemoglobin oxygen affinity (P_{50}) values were normal in the present study.

In contrast to earlier studies in which abnormalities in diffusing capacity have been observed in nondiabetic hyperlipidemic patients[14] and in subjects receiving infusions of artificial triglyceride emulsion,[15] no defects in single breath diffusing capacity or in routine spirometry were observed in the present study in either group of patients. However, our findings are consistent with those of Newball et al., who demonstrated normal diffusing capacities in a group of nondiabetic subjects with a comparable degree of hypertriglyceridemia.[28] Thus, there does not appear to be any firm evidence to support either hypoxemia, impaired oxygen delivery to the tissues by erythrocytes, or impaired oxygen diffusion in the lung in hypertriglyceridemia.

Another aim of this study was to confirm whether factors in addition to uncontrolled diabetes contribute to the marked hypertriglyceridemia sometimes seen with uncontrolled non-insulin-dependent diabetes mellitus.[7,29] The presence of marked lipemia in a fasting plasma specimen was chosen as a prerequisite for entry into the study, since this separates the syndrome of "diabetic lipemia" from the more modest elevation of plasma triglyceride usually seen in association with uncontrolled insulin-dependent and non-insulin-dependent diabetes. All nine diabetic subjects studied had hypertriglyceridemic nondiabetic relatives, with sufficient family members available to enable a definitive genetic diagnosis to be made by established criteria in six instances. In the patient with broad-beta disease and diabetes, it is possible that chylomicron remnants accumulated rather than chylomicrons. Nonetheless, her clinical features did not differ from the other subjects. The fact that every subject had hypertriglyceridemic relatives, taken together with the lower plasma triglyceride levels usually seen in uncontrolled diabetes (usually less than 700 mg/dl),[29] strongly suggests that the coexistence of uncontrolled diabetes and a familial form of hypertriglyceridemia is necessary before marked hypertriglyceridemia results in patients with non-insulin-dependent diabetes. In addition, two patients were on estrogen therapy which can also cause hypertriglyceridemia[21,22] and can interact with familial forms of hypertriglyceridemia to result in chylomicronemia.[7,30] When present in combination in a single patient, these disorders could potentially result in sufficient elevation of the plasma triglyceride pool size so as to saturate the common removal system by which triglycerides of both dietary and endogenous origin are cleared from plasma.[6] Triglyceride-rich lipoproteins of both dietary origin (chylomicrons) or formed endogenously (very low density lipoproteins) would then accumulate. In this study, every patient had some etiologic factor in addition to uncontrolled diabetes as a potential cause of their hypertriglyceridemia.

Studies from our laboratory by Bagdade et al.[31] demonstrated chylomicronemia in four untreated non-insulin-dependent diabetic subjects and in one child who developed ketoacidosis on glucocorticoid therapy. The non-insulin-dependent subjects in that report had fasting plasma glucose and triglyceride levels in the untreated state within the range of values seen in the present study. Originally they hypothesized that the massive hypertriglyceridemia was due entirely to the untreated diabetes mellitus; however, familial forms of hypertriglyceridemia were not sought after. Subsequent studies of the available non-insulin-dependent subjects initially reported[31] revealed that moderate hypertriglyceridemia persisted after treatment of their diabetes. Also, familial forms of hypertriglyceridemia were found in their nondiabetic relatives. Thus, the "diabetic lipemia" as originally described in non-insulin-dependent diabetes appears to be the same as we report here. Whether or not massive hypertriglyceridemia can occur in untreated insulin-dependent diabetes with ketoacidosis without a concomitant familial form of hypertriglyceridemia is unknown. The low prevalence of marked hypertriglyceridemia in ketoacidosis may indicate that two independent diseases are also necessary for the development of marked hypertriglyceridemia in insulin-dependent diabetes.

Thus, certain features seen in association with "diabetic lipemia," i.e., abdominal pain, pancreatitis, eruptive xanthomata, memory loss, dementia, and disturbance of logical thought appear to be reversible and related to the chylomicrons accumulating in plasma rather than to the uncontrolled diabetic state. The presence of any of these symptoms in a diabetic patient should arouse suspicion as to the possible existence of the "chylomicronemia syndrome." If confirmed, other potential causes of hypertriglyceridemia should be sought and appropriately treated if found. Because of the strong possibility that the patient also has a coexisting familial form of hypertriglyceridemia, lipid-lowering therapy with clofibrate often is required in addition to diabetes control, so as to maintain the plasma triglycerides at a sufficiently low level to prevent manifestations of this syndrome.

ACKNOWLEDGMENTS: This research was supported in part by NIH grants AM-02456 and HL-18687. This study was performed at the University Hospital Clinical Research Center (RR-37). A. C. is a recipient of a U. S. Public Health Service Special Emphasis Research Career Award in Diabetes/Cardiovascular (K01 AM 00592).

From the Divisions of Metabolism and Endocrinology, and Respiratory Disease, Department of Medicine, University of Washington, Seattle, Washington.

Address reprint requests to Alan Chait, Division of Metabolism and Endocrinology, RG-20, University of Washington, Seattle, Washington 98195.

REFERENCES

[1] Robinson, D. S.: The function of the plasma triglycerides and fatty acid transport. *In* Comprehensive Biochemistry. Florkin, M., and Stotz, E. M., Eds. Amsterdam, Elsevier, 1970, pp. 81–116.

[2] Pykälistö, O. J., Smith, P. H., and Brunzell, J. D.: Determinants of human adipose tissue lipoprotein lipase. Effect of diabetes and obesity on basal- and diet-induced activity. J. Clin. Invest. *56:* 1108–17, 1975.

[3] Brunzell, J. D., Porte, D., Jr., and Bierman, E. L.: Abnormal lipoprotein lipase mediated plasma triglyceride removal in untreated diabetes mellitus with hypertriglyceridemia. Metabolism *28:* 897–903, 1979.

[4] Harlan, W. T., Jr., Winesett, P. S., and Wasserman, A. T.: Tissue lipoprotein lipase in normal individuals and in individuals with exogenous hypertriglyceridemia and the relationship of this enzyme to the assimilation of fat. J. Clin. Invest. *46:* 239–47, 1967.

[5] Goldberg, A. P., Chait, A., and Brunzell, J. D.: Postprandial adipose tissue lipoprotein lipase in primary hypertriglyceridemia. Metabolism *29:* 223–29, 1980.

[6] Brunzell, J. D., Hazzard, W. R., Porte, D., Jr., et al.: Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. J. Clin. Invest. *52:* 1578–85, 1973.

[7] Brunzell, J. D., and Schrott, H. G.: The interaction of familial and secondary causes of hypertriglyceridemia: role in pancreatitis. Trans. Assoc. Am. Physicians *86:* 245–54, 1973.

[8] Frederickson, D. S., and Levy, R. I.: Familial hyperlipoproteinemia. *In* Metabolic Basis of Inherited Disease. Stanbury, J. B., Wyngaarden, J. B., and Fredrickson, D. S., Eds. New York, McGraw-Hill, 1972, pp. 545–614.

[9] Greenberger, N. J., Hatch, F. T., Drummery, G. D., et al.: Pancreatitis and hyperlipemia: a study of serum lipid alterations in 25 patients with acute pancreatitis. Medicine *45:* 161–74, 1966.

[10] Cameron, J. L., Capuzzi, D. M., Zuidema, G. D., et al.: Acute pancreatitis with hyperlipidemia—evidence for a persistent defect in lipid metabolism. Am. J. Med. 56: 482–87, 1974.

[11] Kuo, P. T., and Whereat, A. F.: Lipemia as a cause of arterial oxygen unsaturation and the effect of its control in patients with atherosclerosis. Circulation *16:* 493, 1957.

[12] Talbot, G. D., and Frayser, R.: Hyperlipidaemia: a cause of decreased oxygen saturation. Nature *200:* 684, 1963.

[13] Ditzel, J., and Dyerberg, J.: Hyperlipoproteinemia, diabetes, and oxygen affinity of hemoglobin. Metabolism 26: 141–50, 1977.

[14] Enzi, G., Bevilacqua, M., and Crepaldi, G.: Disturbances in pulmonary gaseous exchange in primary hyperlipoproteinemias. Bull. Eur. Physiol. Resp. *12:* 433–42, 1976.

[15] Sundström, G., Zauner, C. W., and Arborelius, M., Jr.: Decrease in pulmonary diffusing capacity during lipid infusion in healthy men. J. Appl. Physiol. *34:* 816–20, 1973.

[16] Heilman, K. M., and Fisher, W. D.: Hyperlipidemic dementia. Arch. Neurol. *31:* 67–68, 1974.

[17] Mathew, N. T., Meyer, J. S., Achari, A. N., et al.: Hyperlipidemic neuropathy and dementia. Eur. Neurol. *14:* 370–82, 1976.

[18] Lipid Research Clinics Manual of Laboratory Operations. Washington, D. C., U. S. Department of Health, Education and Welfare, 1974.

[19] Havel, R. J.: Pathogenesis, differentiation and management of hypertriglyceridemia. Adv. Intern. Med. *15:* 117–54, 1969.

[20] O'Hara, D. D., Porte, D., Jr., and Williams, R. H.: Use of constant composition polyvinylpyrrolidone columns to study the interaction of fat particles with plasma. J. Lipid Res. *7:* 264–69, 1966.

[21] Chait, A.: Secondary hyperlipidaemia. J. Clin. Pathol. *26* (Suppl. 5): 68–71, 1973.

[22] Brunzell, J., Chait, A., and Bierman, E. L.: Pathophysiology of lipoprotein transport. Metabolism *27:* 1109–27, 1978.

[23] Brunzell, J. D., Schrott, H. G., Motulsky, A. G., et al.: Myocardial infarction in the familial forms of hypertriglyceridemia. Metabolism *25:* 313–20, 1976.

[24] Godfrey, S., Wozniak, E. R., Courtenay-Evans, R. J., et al.: Ear lobe blood samples for blood gas analysis at rest and during exercise. Br. J. Dis. Chest *65:* 58–64, 1971.

[25] Bellingham, A. J., and Lenfant, C.: Hb affinity for O_2 determined by O_2-Hb dissociation analyzer. J. Appl. Physiol. 30: 903–904, 1971.

[26] Detter, J. C., Gibson, D. F., MacMillan, S. F., et al.: Manual determination of intraerythrocytic 2,3-diphosphoglycerate in whole blood by enzymatic analysis, and comparison with ion exchange chromatography. Clin. Chem. *21:* 376–80, 1975.

[27] Robertson, H. T., Chait, A., Hlastala, M., et al.: Red cell oxygen affinity in severe hypertriglyceridemia. Proc. Soc. Exp. Biol. Med. *159:* 437–40, 1978.

[28] Newball, H. H., Friedewald, W. T., Roberts, B., et al.: Effect of elevated triglyceride on the diffusing capacity of man. Am. Rev. Resp. Dis. *112:* 83–87, 1975.

[29] Brunzell, J. D., Hazzard, W. R., Motulsky, A. G., and Bierman, E. L.: Evidence for diabetes mellitus and genetic forms of hypertriglyceridemia as independent entities. Metabolism *24:* 1115–21, 1975.

[30] Glueck, C. J., Scheel, D., Fishback, J., et al.: Estrogen-induced pancreatitis in patients with previously covert familial type V hyperlipoproteinemia. Metabolism *21:* 657–66, 1972.

[31] Bagdade, J. D., Porte, D., and Bierman, E. L.: Diabetic lipemia, a form of acquired fat-induced lipemia. N. Engl. J. Med. *276:* 427–33, 1967.