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Lipoprotein metabolism: A review

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Abstract
The knowledge of plants used in traditional medicine by the indigenous communities is fast disappearing due to various reasons. This study made an effort to document the herbal knowledge that exists in the family circles of the Yucatec Maya communities of Northern Belize. Research was carried out in four villages in the Corozal and Orange Walk Districts during 12 weeks of fieldwork. A total of 59 plant species, grouped within 57 genera and 35 families that are used in traditional medical practices were identified and studied. Plants belonging to Rutaceae, Lamiaceae and Euphorbiaceae were the most commonly used species. The growth habits of plants reported include herbs (37%), trees (25%), shrubs (15%), trees/shrubs (plants having characteristics of both trees and shrubs) (14%), and vines (9%). The most common plant part used was leaves (66%), followed by bark, whole plant and flower (each with 7%). Of the total number of medicinal plants, 20 species were used to treat infections, 16 for digestive system disorders, 9 for skin/subcutaneous cellular tissue disorders, 7 for respiratory system disorders, 6 for endocrine system disorders, 6 for culture-bound syndromes, 5 for genitourinary system disorders, 4 for musculoskeletal system disorders, 4 for circulatory system disorders, 2 for injuries and 1 for sensory system disorders. Species cited more frequently by the most herbalists are regarded to be of greater ethnobotanical importance than those cited only by a few herbalists.

Keywords: Lipoprotein, disorders

Introduction
Cholesterol and triglyceride are indispensable structural and metabolic components of all animal cells. Since they're hydrophobic they needs to be transported through the aqueous setting of the plasma, during a shell of phospholipid and special proteins known as apoliporpoteins, forming a family of lipid protein particles or lipoproteins. The apolipoproteins play vital role not only in maintaining the structure of the particles however additionally in guiding their metabolism by acting as recognition proteins for a range of plasma enzymes and cell membrance receptors [1].

Lipoprotein metabolism is a through of in items of 3 interconnected transport pathways specializing in the liver. Once, the exogenous pathway, is chargeable for the digestion, absorption and tissue dissemination of dietary fat. About hundred g. of triglyceride and 0.5 g of cholesterol flow through it every day. Biological process enzymes in the intestinal lumen hydrolyse these fats to free cholesterol, fatty acids and mono and diglycerides, which combine with bile salts to form the water soluble micelles responsible for carrying the lipids to absorptive sites in the small intestine. Under normal circumstances triglyceride absorption is virtually complete, while only about 50% of the cholesterol is taken up the rest being lost in the faces (Figure 1).

Lipoproteins are complexes of lipids and proteins that are essential for the transport of cholesterol, triglycerides, and fat-soluble vitamins. Until recently, lipoprotein disorders were the purview of lipidologists, but the demonstration that lipid-lowering therapy significantly reduces the clinical complications of atherosclerotic cardiovascular disease (ASCVD) has brought the diagnosis and treatment of these disorders into the domain of the general internist. The metabolic consequences associated with changes in diet and lifestyles have increased the number of hyperlipidemic individuals who could benefit from lipid lowering therapy [2]. The development of safe, effective, and well tolerated pharmacologic agents has greatly expanded the therapeutic armamentarium available to the physician to treat disorders of lipid metabolism. Therefore, the appropriate diagnosis and management of lipid disorders is critically important to the practice of medicine. This chapter reviews normal lipoprotein physiology, the pathophysiology of the known single gene disorders of lipoprotein metabolism, the environmental factors that influence lipoprotein metabolism, and the practical approaches to their diagnosis and management [3].

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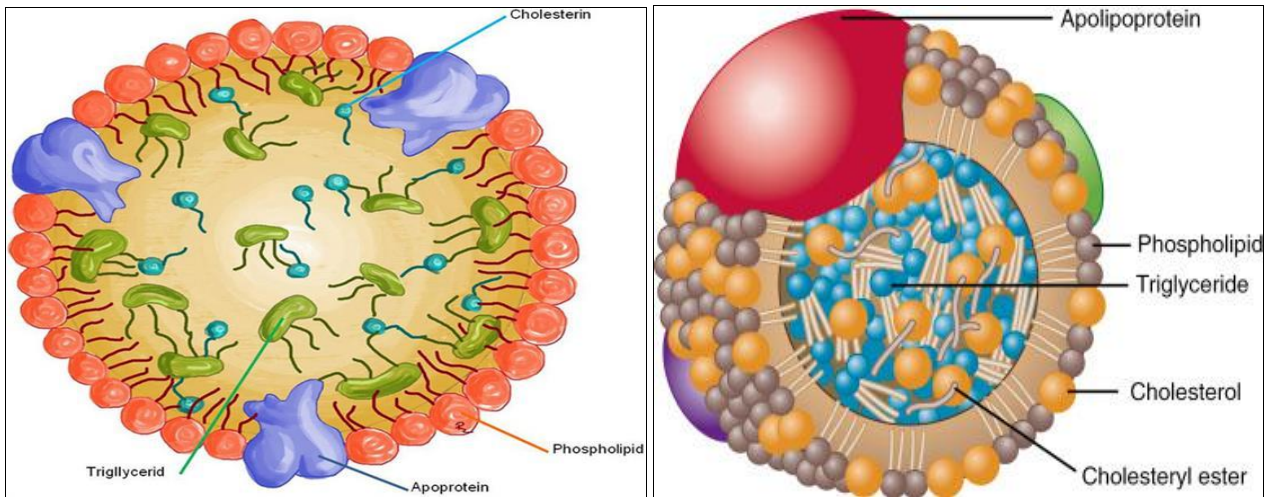Ganganagar, Rajasthan, India

Fig 1: Structure of a lipoprotein

Lipoproteins are large, mostly spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters, and fat soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues. Lipoproteins play an essential role in the absorption of dietary cholesterol, long chain fatty acids, and fat soluble vitamins; the transport of triglycerides, cholesterol, and fat soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver. Lipoproteins contain a core of hydrophobic lipids (triglycerides and cholesteryl esters) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids [4].

The plasma lipoproteins are divided into five major classes based on their relative densities: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL) (Table 1). Each lipoprotein class comprises a family of particles that vary slightly in density, size, migration during electrophoresis, and protein composition. The density of a lipoprotein is determined by the amount of lipid and protein per particle. HDL is the smallest and most dense lipoprotein, whereas chylomicrons and VLDL are the largest and least dense lipoprotein particles. Most triglyceride is transported in chylomicrons or VLDL, and most cholesterol is carried as cholesteryl esters in LDL and HDL. The apolipoproteins are required for the assembly and structure of lipoproteins. Apolipoproteins also serve to activate enzymes important in lipoprotein metabolism and to mediate the binding of lipoproteins to cell-surface receptors. ApoA-I, which is synthesized in the liver and intestine, is found on virtually all HDL particles [5]. ApoA-II is the second most abundant HDL apolipoprotein and is found on approximately two thirds of all HDL particles. ApoB is the major structural protein of chylomicrons, VLDL, IDL, and LDL; one molecule of apoB, either apoB-48 (chylomicrons) or apoB-100 (VLDL, IDL, or LDL), is present on each lipoprotein particle. The human liver makes only apoB-100, and the intestine makes apoB-48, which is derived from the same gene by mRNA editing. ApoE is present in multiple copies on chylomicrons, VLDL, and IDL and plays a critical role in the metabolism and clearance of triglyceride-rich particles [6, 7]. Three apolipoproteins of the C-series (apoC-I, -II, and -III) also participate in the metabolism of triglyceride rich lipoproteins.

Table 1: Classification of the hyperlipoproteinamias

Lipoprotein class	Density (g mL⁻¹)	Diameter (nm)	% Protein	% Cholesterol	% Phospholipid	% Triglycerides
HDL	1.063–1.210	5–15	33	30	29	8
LDL	1.019–1.063	18–28	25	50	21	4
IDL	1.006–1.019	25–50	18	29	22	31
VLDL	0.95–1.006	30–80	10	22	18	50
Chylomicrons	<0.95	100–1000	<2	8	7	84

The exogenous pathway of lipoprotein metabolism permits efficient transport of dietary lipids. Dietary triglycerides are hydrolyzed by pancreatic lipases within the intestinal lumen and are emulsified with bile acids to form micelles. Dietary cholesterol and retinol are esterified (by the addition of a fatty acid) in the enterocyte to form cholesteryl esters and retinyl esters, respectively. Longer chain fatty acids (12 carbons) are incorporated into triglycerides and packaged

with apoB- 48, cholesteryl esters, retinyl esters, phospholipids, and cholesterol to form chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver. The particles encounter lipoprotein lipase (LPL), which is anchored to proteoglycans that decorate the capillary endothelial surfaces of adipose tissue, heart, and skeletal muscle. The triglycerides of chylomicrons are hydrolyzed by LPL, and free fatty acids are released; apoC-II, which is transferred to circulating chylomicrons, acts as a cofactor for LPL in this reaction. The released free fatty acids are taken up by adjacent myocytes or adipocytes and either oxidized or reesterified and stored as triglyceride. Some free fatty acids bind albumin and are transported to other tissues, especially the liver. The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids (cholesterol and phospholipids) on the particle surface are transferred to HDL. The resultant smaller, more cholesterol ester–rich particles are referred to as chylomicron remnants. The remnant particles are rapidly removed from the circulation by the liver in a process that requires apoE. Consequently, few, if any, chylomicrons are present in the blood after a 12 h fast, except in individuals with disorders of chylomicron metabolism [8].

The endogenous pathway of lipoprotein metabolism refers to the hepatic secretion and metabolism of VLDL to IDL and LDL. VLDL particles resemble chylomicrons in protein composition but contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to triglyceride (1 mg of cholesterol for every 5 mg of triglyceride). The triglycerides of VLDL are derived predominantly from the esterification of long chain fatty acids. The packaging of hepatic triglycerides with the other major components of the nascent VLDL particle (apoB-100, cholesteryl esters, phospholipids, and vitamin E) requires the action of the enzyme microsomal transfer protein (MTP). After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series. The triglycerides of VLDL are hydrolyzed by LPL, especially in muscle and adipose tissue. As VLDL remnants undergo further hydrolysis, they continue to shrink in size and become IDL, which contain similar amounts of cholesterol and triglyceride. The liver removes approximately 40 to 60% of VLDL remnants and IDL by LDL receptor mediated endocytosis via binding to apoE. The remainder of IDL is remodeled by hepatic lipase (HL) to form LDL; during this process, most of the triglyceride in the particle is hydrolyzed and all apolipoproteins except apoB-100 are transferred to other lipoproteins. The cholesterol in LDL accounts for 70% of the plasma cholesterol in most individuals [9]. Approximately 70% of circulating LDLs are cleared by LDL receptor–mediated endocytosis in the liver.
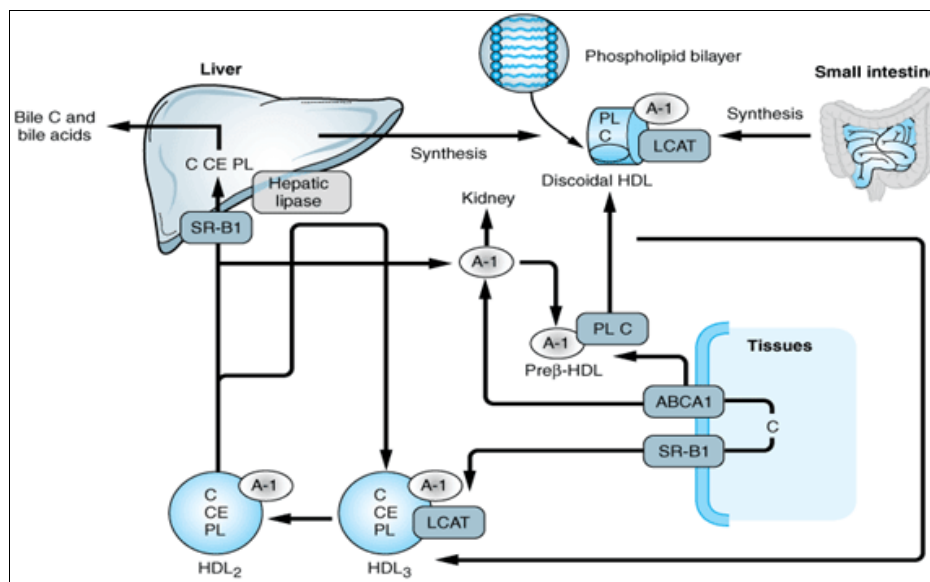

Fig 2: HDL metabolism and reverse cholesterol transport

Lipoprotein (a) [Lp(a)] is a lipoprotein similar to LDL in lipid and protein composition, but it contains an additional protein called apolipoprotein(a) [apo(a)]. Apo(a) is synthesized in the liver and is attached to apoB-100 by a disulfide linkage. The mechanism by which Lp(a) is removed from the circulation is not known. All nucleated cells synthesize cholesterol but only hepatocytes can efficiently metabolize and excrete cholesterol from the body. The predominant route of cholesterol elimination is by excretion into the bile, either directly or after conversion to bile acids. Cholesterol in peripheral cells is transported from the plasma membranes of peripheral cells to the liver by an HDL mediated process termed reverse cholesterol transport. Nascent HDL particles are synthesized by the intestine and the liver (Figure 2). The newly formed discoidal HDL particles contain apoA-I and phospholipids (mainly lecithin) but rapidly acquire unesterified cholesterol and additional phospholipids from peripheral tissues via transport by the membrane protein ATP binding cassette protein A1 (ABCA1). Once incorporated in the HDL particle, cholesterol is esterified by lecithin cholesterol acyltransferase (LCAT), a plasma enzyme associated with HDL. As HDL acquires more cholesteryl ester it becomes spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDL during lipolysis. HDL cholesterol is transported to hepatoctyes by both an indirect and a direct pathway. HDL cholesteryl esters are transferred to apoB containing lipoproteins in exchange for triglyceride by the cholesteryl ester transfer protein (CETP). The cholesteryl

esters are then removed from the circulation by LDL receptor–mediated endocytosis [10]. HDL cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class BI (SR-BI), a cell surface receptor that mediates the selective transfer of lipids to cells. HDL particles undergo extensive remodeling within the plasma compartment as they transfer lipids and proteins to lipoproteins and cells. For example, after CETP mediated lipid exchange, the triglyceride enriched HDL becomes a substrate for HL, which hydrolyzes the triglycerides and phospholipids to generate smaller HDL particles.

Disorders of lipoprotein metabolism
The identification and characterization of genes responsible for the genetic forms of hyperlipidemia have provided important molecular insight into the critical roles of apolipoproteins, enzymes, and receptors in lipid metabolism.

Abetalipoproteinemia Abetalipoproteinemia is a rare autosomal recessive disease caused by mutations in the gene encoding MTP, which transfers lipids to nascent chylomicrons and VLDL in the intestine and liver, respectively. Plasma cholesterol and triglyceride levels are extremely low in this disorder, and no chylomicrons, VLDL, LDL, or apoB are detectable. The parents of patients with abetalipoproteinemia (who are obligate heterozygotes) have normal plasma lipid and apoB levels. Abetalipoproteinemia usually presents in early childhood with diarrhea and failure to thrive and is characterized clinically by fat malabsorption, spinocerebellar degeneration, pigmented retinopathy, and acanthocytosis. The initial neurologic manifestations are loss of deep tendon reflexes, followed by decreased distal lower extremity vibratory and proprioceptive sense, dysmetria, ataxia, and the development of a spastic gait, often by the third or fourth decade. Patients with abetalipoproteinemia also develop a progressive pigmented retinopathy presenting with decreased night and color vision, followed by reductions in daytime visual acuity and ultimately progressing to near blindness. The presence of spinocerebellar degeneration and pigmented retinopathy in this disease has resulted in misdiagnosis of Friedreich's ataxia. Rarely, patients with abetalipoproteinemia develop a cardiomyopathy with associated life threatening arrhythmias. Most clinical manifestations of abetalipoproteinemia result from defects in the absorption and transport of fat soluble vitamins. Vitamin E and retinyl esters are normally transported from enterocytes to the liver by chylomicrons, and vitamin E is dependent on VLDL for transport out of the liver and into the circulation. Patients with abetalipoproteinemia are markedly deficient in vitamin E and are also mildly to moderately deficient in vitamin A and vitamin K. Treatment of abetalipoproteinemia consists of a low fat, high caloric, vitamin enriched diet accompanied by large supplemental doses of vitamin E. It is imperative for treatment to be initiated as soon as possible to obviate the development of neurologic sequelae [11, 12].

Familial Hypobetalipoproteinemia
Familial homozygous hypobetalipoproteinemia has a clinical picture similar to abetalipoproteinemia but is autosomal codominant in inheritance pattern. The disease can be differentiated from abetalipoproteinemia since the parents of the probands with this disorder have levels of plasma LDL-C and apoB that are less than half of the normal levels. Mutations in the gene encoding apoB-100 that interfere with protein synthesis are common causes of this disorder. These patients, like those with abetalipoproteinemia, should be referred to specialized.

Hepatic Lipase Deficiency
HL is a member of the same gene family as LPL and hydrolyzes triglycerides and phospholipids in remnant lipoproteins and HDL. HL deficiency is a very rare autosomal recessive disorder characterized by elevated plasma cholesterol and triglycerides (mixed hyperlipidemia) due to the accumulation of lipoprotein remnants. HDL-C is normal or elevated. The diagnosis is confirmed by measuring HL activity in post heparin plasma. Due to the small number of patients with HL deficiency, the association of this genetic defect with ASCVD is not known, but lipid lowering therapy is recommended.

Autosomal Recessive Hypercholesterolemia
Autosomal recessive hypercholesterolemia (ARH) is a rare disorder (except in Sardinia) due to mutations in a protein (ARH) involved in LDL receptor mediated endocytosis in the liver. ARH clinically resembles homozygous FH and is characterized by hypercholesterolemia, tendon xanthomas, and premature coronary artery disease. The hypercholesterolemia tends to be intermediate between the levels seen in FH homozygotes and FH heterozygotes. LDL receptor function in cultured fibroblasts is normal or only modestly reduced in ARH, whereas LDL receptor function in lymphocytes and the liver is negligible. Unlike FH homozygotes, the hyperlipidemia responds partially to treatment with HMG-CoA reductase inhibitors, but these patients usually require LDL apheres is to lower plasma LDL C to recommended levels.

Familial Hypercholesterolemia
Familial hypercholesterolemia is an autosomal codominant disorder characterized by elevated plasma LDL C with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Familial hypercholesterolemia is caused by 750 mutations in the LDL receptor gene and has a higher incidence in certain populations, such as Afrikaners, Christian Lebanese, and French Canadians, due to the founder effect. The elevated levels of LDL C in Familial hypercholesterolemia are due to delayed catabolism of LDL and its precursor particles from the blood, resulting in increased rates of LDL production. There is a major gene dose effect, in that individuals with two mutated LDL receptor alleles (Familial hypercholesterolemia homozygotes) are much more affected than those with one mutant allele (Familial hypercholesterolemia heterozygotes).

Familial Combined Hyperlipidemia
The molecular etiology of familial combined hyperlipidemia is unknown but is likely to involve defects in several different genes familial combined hyperlipidemia is the most common primary lipid disorder, occurring in approximately 1 in 200 persons. Approximately 20% of patients who develop CHD before age 60 have familial combined hyperlipidemia.

Polygenic Hypercholesterolemia
Polygenic hypercholesterolemia is characterized by

hypercholesterolemia with a normal plasma triglyceride in the absence of secondary causes of hypercholesterolemia. Plasma LDL-C levels are not as elevated as they are in FH and FDB. Family studies are useful to differentiate polygenic hypercholesterolemia from the single gene disorders described above; half of the first degree relatives of patients with FH and FDB are hypercholesterolemic, whereas 10% of first degree relatives of patients with polygenic hypercholesterolemia are hypercholesterolemic.

Treatment of polygenic hypercholesterolemia is identical to that of other forms of hypercholesterolemia.

Secondary Disorders of Lipoprotein Metabolism
Significant changes in plasma levels of lipoproteins are seen in a variety of diseases. It is critical that secondary causes of hyperlipidemias are considered prior to initiation of lipid lowering therapy (Table 2).

Table 2: Secondary Forms of Hyperlipidemia

LDL ELEVATED	LDL REDUCED	HDL ELEVATED	HDL REDUCED	VLDL ELEVATED	IDL ELEVATED	CHYLOMICRONS ELEVATED	LP(a) ELEVATED
Hypothyroidism	Severe liver disease	Alcohol	Smoking	Obesity	Multiple myeloma	Autoimmune disease	Renal insufficiency
Nephrotic syndrome	Malabsorption Malnutrition	Exercise Exposure to chlorinated hydrocarbons	DM type 2 Obesity	DM type 2 Glycogen storage disease	Monoclonal gammopathy	DM type 2	Inflammation
Cholestasis	Gaucher's disease		Malnutrition				Menopause
Acute intermittent porphyria	Chronic infectious disease	Drugs: estrogen	Gaucher's disease	Hepatitis Alcohol	Autoimmune disease		Orchidectomy
Anorexia nervosa Hepatoma Drugs: thiazides, cyclosporin, tegretol	Hyperthyroidism Drugs: niacin toxicity		Drugs: anabolic steroids, beta blockers	Renal failure Sepsis Stress Cushing's syndrome Pregnancy Acromegaly Lipodystrophy Drugs: estrogen, beta blockers, glucocorticoids, bile acid binding resins, retinoic acid	Hypothyroidism		Hypothyroidism Acromegaly Nephrosis Drugs: growth hormone, isotretinoin

Abbreviations: DM, diabetes mellitus; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very low-density lipoprotein.

Treatment
Dietary modification is an important component in the management of hyperlipidemia. In the hypercholesterolemic patient, dietary saturated fat and cholesterol should be restricted. For patients who are hypertriglyceridemic, the intake of simple sugars should also be curtailed. For severe hypertriglyceridemia [11.3 mmol/L (1000 mg/dL)], restriction of total fat intake is critical. The most widely used diet to lower the LDL C level is the "Step 1 diet" developed by the American Heart Association. Most patients have a relatively modest (10%) decrease in plasma levels of LDL C on a step I diet in the absence of any associated weight loss. Almost all persons experience a decrease in plasma HDL C levels with a reduction in the amount of total and saturated fat in their diet.

Weight Loss and Exercise
The treatment of obesity, if present, can have a favourable impact on plasma lipid levels and should be actively encouraged. Plasma triglyceride and LDL C levels tend to fall and HDLC levels tend to increase in obese persons who lose weight. Aerobic exercise has a very modest elevating effect on plasma levels of HDLC in most individuals but has cardiovascular benefits that extend beyond the effects on plasma lipid levels.

Conclusion
There is a specific requirement for phosphatidylcholine biosynthesis in support of large scale chylomicron formation and secretion, although smaller amounts of chylomicrons may be secreted by increasing the particle size without expansion of the phospholipid pool. The requirement for phosphatidylcholine biosynthesis during fat absorption is supported by the recent demonstration of an expansion of the mucosal lipid phosphorus pool and appropriate changes in its relative specific activity. Mucosal absorption of dietary fat therefore appears to be a concerted metabolic event involving the entire villus cell rather than a shunt characterized by limited metabolic commitment of the cellular machinery. As a result the involvement of fat absorption and metabolism in the interaction between environmental agents and the alimentary tract must be expected to be complex. To date, very little of this interaction has been documented.

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