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LIVER TRANSPLANTATION TO PROVIDE LOW-DENSITY-LIPOPROTEIN RECEPTORS AND LOWER PLASMA CHOLESTEROL IN A CHILD WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

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Abstract

A six-year-old girl with severe hypercholesterolemia and atherosclerosis had two defective genes at the low-density-lipoprotein (LDL) receptor locus, as determined by biochemical studies of cultured fibroblasts. One gene, inherited from the mother, produced no LDL receptors; the other gene, inherited from the father, produced a receptor precursor that was not transported to the cell surface and was unable to bind LDL. The patient degraded intravenously administered ^{125}I-LDL at an extremely low rate, indicating that her high plasma LDL-cholesterol level was caused by defective receptor-mediated removal of LDL from plasma. After transplantation of a liver and a heart from a normal donor, the patient's plasma LDL-cholesterol level declined by 81 per cent, from 988 to 184 mg per deciliter. The fractional catabolic rate for intravenously administered ^{125}I-LDL, a measure of functional LDL receptors in vivo, increased by 2.5-fold. Thus, the transplanted liver, with its normal complement of LDL receptors, was able to remove LDL cholesterol from plasma at a nearly normal rate.

We conclude that a genetically determined deficiency of LDL receptors can be largely reversed by liver transplantation. These data underscore the importance of hepatic LDL receptors in controlling the plasma level of LDL cholesterol in human beings.

Familial hypercholesterolemia is caused by mutations in the gene encoding the low-density-lipoprotein (LDL) receptor. This cell-surface receptor normally removes cholesterol-carrying LDL from the circulation. [1] Persons with two mutant LDL-receptor genes (homozygous familial hypercholesterolemia) produce few or no LDL receptors and therefore remove LDL from plasma at a reduced rate. As a result, LDL accumulates in plasma to levels up to eight times normal, and total plasma cholesterol levels frequently reach 1000 mg per deciliter (30 mmol per liter). These patients almost always have severe atherosclerosis in childhood, with death from myocardial infarction often occurring before the age of 20.[2]

The heterozygous form of familial hypercholesterolemia, in which a single mutant LDL-receptor gene is inherited, occurs at a frequency of 1 in 500 in the general population. Affected persons produce on average about half the normal number of LDL receptors.[2] LDL accumulates to twice the normal level, and symptomatic atherosclerosis usually occurs in the fourth and

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fifth decades of life. Typically, each heterozygote for familial hypercholesterolemia will transmit the mutant gene to half of his or her children, who then become heterozygotes. When two heterozygotes marry (as occurs in 1 of 250,000 marriages), one fourth of the offspring will inherit a copy of the mutant LDL-receptor gene from both parents, and these offspring will be homozygotes.

Considerable progress has been made in the understanding of familial hypercholesterolemia at the basic and clinical levels. The LDL receptor has been purified, and specific antibodies have been obtained.[3] The messenger RNA and the gene for the LDL receptor have been cloned, and the amino acid sequence of the protein has been deduced.[4] The human gene has been localized to chromosome 19.[5]

Biosynthetic studies have revealed that the LDL receptor is synthesized as a glycoprotein precursor that has an apparent molecular weight of 120,000.[6,7] Within 30 minutes after synthesis, the receptor is transported to the Golgi complex, where its carbohydrate chains are elongated. After this processing, the migration of the receptor on sodium dodecyl sulfate gels is retarded, so that it corresponds to an apparent molecular weight of 160,000. A few minutes later the receptor appears on the cell surface, where it binds to LDL and clusters in coated pits, carrying the bound LDL into the cell for degradation.

At least eight mutant alleles (genes) at the LDL-receptor locus have been identified in patients with familial hypercholesterolemia.[6,8,9] The most common allele (the so-called null allele) produces no detectable receptors. Another allele produces a receptor that is synthesized as a 120,000-dalton precursor that cannot be transported to the Golgi complex. These mutant receptors do not undergo the carbohydrate-processing reactions, and hence they do not increase in apparent molecular weight. Since they do not reach the cell surface, they cannot bind extracellular LDL and hence they are nonfunctional. Other alleles produce mutant receptors that bind small amounts of LDL. Many homozygotes with familial hypercholesterolemia have inherited different alleles from each parent, and hence they are not true homozygotes but rather compound heterozygotes, analogous to patients with two mutant β-globin genes, as in sickle C disease.

Treatment of familial hypercholesterolemia in homozygotes has been unsatisfactory since most of the manipulations that lower plasma LDL concentrations act by stimulating normal genes in the liver to produce more LDL receptors.[10,11] The possibility of an improved treatment has been raised by two recent advances: the recognition that up to three fourths of the total LDL receptors in the body are located in the liver, and progress in surgical and immunologic techniques for liver transplantation. The liver manufactures large numbers of LDL receptors because it requires large amounts of cholesterol for secretion into bile, for conversion to bile acids, and for the production of lipoproteins.[12–15] For this reason, transplantation of a normal liver with its normal receptors should theoretically lower LDL levels profoundly in homozygotes.[1]

On the basis of this rationale, liver transplantation was recently performed in a six-year-old girl with homozygous familial hypercholesterolemia.[16] Two previous coronary bypass operations and mitral-valve replacement (necessitated by papillary-muscle dysfunction) had failed to arrest her progressive coronary-artery disease. Accordingly, she underwent combined liver–heart transplantation. Starzl et al. recently described the clinical aspects of this case and reported that the liver–heart transplantation led to a marked decrease in the patient's plasma cholesterol level.[16] In the current paper, we describe the biochemical defect in this patient's cells and report the results of in vivo studies designed to determine whether the liver transplantation lowered her plasma LDL level by providing a new source of LDL receptors.

Methods

Clinical Data

The six-year-old girl with homozygous familial hypercholesterolemia is designated as Patient FH 728. Her clinical history has been reported elsewhere.[16] In September 1983 the diagnosis of homozygous familial hypercholesterolemia was established, and she was admitted to the General Clinical Research Center at the University of Texas Health Science Center at Dallas, where she underwent a lipoprotein-turnover study while receiving no medications. Her plasma cholesterol level was above 1000 mg per deciliter (30 mmol per liter). Shortly thereafter, she had a myocardial infarction; continuing angina required two coronary bypass operations. During the second operation her mitral valve was replaced because of papillary-muscle dysfunction. Angina continued. In February 1984, her liver and heart were replaced with a liver and heart from a single donor. The transplant operation was performed at the University of Pittsburgh Health Center after approval by the Human Rights Institutional Review Board of the Children's Hospital of Pittsburgh.[16]

In June 1984, the patient was readmitted to the General Clinical Research Center in Dallas for a repeat study of ^{125}I-LDL turnover. The second study was carried out while she was taking the following daily medications: cydosporine, 150 to 200 mg; prednisone, 7.5 mg; captopril, 25 mg; and furosemide (Lasix), 40 mg. The two studies of lipoprotein turnover were performed under the guidelines of the Human Research Committee of the University of Texas Health Science Center at Dallas.

Cultured Cells

Human fibroblasts were obtained from skin-biopsy specimens and grown in monolayer culture at 37°C in a 5 per cent carbon dioxide incubator. Cells from stock cultures were seeded into 60-mm Petri dishes according to a standard protocol and cultured for five to six days; maximal synthesis of LDL receptors was induced by incubation in human lipoprotein-deficient serum for 16 to 48 hours before study, as described elsewhere.[17]

Assays of LDL Metabolism in Fibroblasts

Human LDL (density, 1.019 to 1.063 g per milliliter) was prepared by ultracentrifugation, and LDL was radiolabeled with ^{125}I by the iodine monochloride method.[17] Cells were incubated in medium containing 10 per cent (vol/vol) lipoprotein-deficient serum for 48 hours before assay. We then measured the binding of ^{125}I-LDL to fibroblast monolayers at 4°C; the binding, internalization, and degradation of ^{125}I-LDL by monolayers at 37°C; and the incorporation of [^{14}C]oleate into cholesteryl [^{14}C]esters.[17]

Incorporation of [^{35}S]Methionine into LDL Receptors

After incubation for 16 hours in medium containing 10 per cent lipoprotein-deficient serum, cells were switched to methionine-free Dulbecco's modified Eagle medium containing 10 per cent lipoprotein-deficient serum. [^{35}S]Methionine (100 μCi per milliliter [100 to 150 Ci per millimole]) was added for various times as indicated in the figure legends (pulse). The radioactive medium was then removed, and the cells were incubated in complete Dulbecco's modified Eagle medium (final methionine concentration, 0.1 mM) for the indicated times (chase). The monolayers were washed and lysed, and LDL receptors were precipitated by incubation with immune complexes containing either antireceptor monoclonal antibody IgG-C7 or a control monoclonal antibody, IgG-2001, as described by Tolleshaug et al.[6] The washed immunoprecipitates were dissolved in 8 M urea and 0.2 M dithiothreitol and subjected to electrophoresis in sodium dodecyl sulfate polyacrylamide gels, followed by fluorography for

four days.[6] Gels were calibrated with molecular-weight standards ranging from 68,000 to 200,000.[6]

Lipoprotein-Turnover Studies

Studies of lipoprotein turnover were carried out as described elsewhere.[18] Patient FH 728 was given a partial solid-food diet with a caloric distribution of 40 per cent fat (polyunsaturated to saturated ratio of 0.33), 40 per cent carbohydrate, and 20 per cent protein. The cholesterol intake was limited to 250 mg per day. Each study was initiated by intravenous injection of 2 ml of a mixture of 14 μCi of autologous ^{125}I-LDL, unlabeled native LDL (2 mg), and human serum albumin (150 mg). Kinetic indexes for the disappearance of LDL were calculated by the two-pool model of Matthews[19] with the SAAM computer program.[20]

Results

Fibroblasts from the patient bound, internalized, and degraded less than 5 per cent of the normal amount of ^{125}I-LDL (Table 1, Experiment A). Fibroblasts from the normal donor of the liver and heart bound, internalized, and degraded a normal amount of ^{125}I-LDL (Table 1, Experiment B). Similar results were obtained when we measured the amount of cell-surface binding at 4° C (data not shown).

A functional test of LDL uptake through the receptor mechanism is the stimulation of cholesteryl-ester formation. [21] Fibroblasts grown in the absence of LDL have no excess sterols and hence fail to incorporate [^{14}C]oleate into cholesteryl [^{14}C]oleate. When the cells are incubated with LDL, the incorporation of [^{14}C]oleate into cholesteryl esters is enhanced. Esterification can also be stimulated by incubating the cells with 25-hydroxycholesterol, which enters cells and stimulates cholesteryl-ester synthesis without a requirement for the LDL receptor. To estimate LDL-receptor function, we compared the stimulation of cholesteryl-ester synthesis produced by 25-hydroxy-cholesterol with the stimulation produced by LDL.[21] As shown in Table 2, normal cells had a 3.1-fold higher rate of cholesterol esterification when incubated with LDL than when incubated with 25-hydroxycholesterol. In the patient's cells, 25-hydroxycholesterol had a normal stimulatory effect, but LDL was completely ineffective.

Both parents of Patient FH 728 had elevated LDL-cholesterol levels (>95th percentile), as expected in heterozygotes for familial hypercholesterolemia. The values for total and LDL cholesterol in the mother, age 26 years, were 227 and 172 mg per deciliter (5.87 and 4.45 mmol per liter); the corresponding values in the father, age 36 years, were 324 and 253 mg per deciliter (8.38 and 6.54 mmol per liter). In fibroblasts from both parents, LDL was about half as effective as it was in the normal subject in stimulating cholesterol esterification (Table 2). The relative rates of esterification in these two obligate heterozygotes were within the range previously observed for other heterozygotes,[21] indicating that both parents produced about half the normal number of functional LDL receptors. A similar reduction in LDL-receptor activity was noted when the binding, internalization, and degradation of ^{125}I-LDL were measured in fibroblasts (data not shown).

To study the structural basis of the receptor defect in the patient's fibroblasts, we incubated the cells for one hour with [^{35}S]methionine and then incubated them with unlabeled methionine for 15 minutes or two hours, after which we solubilized the cells in detergents and immunoprecipitated the LDL receptors (Fig. 1). In the normal cells after the 15-minute chase period, about half the receptors were in the precursor form (120,000 daltons), and half were in the mature form (160,000 daltons) (Fig. 1, Lane A). After another two-hour incubation, all the receptors had undergone processing and were in the mature form (Lane B). The patient's cells synthesized a relatively small number of immunoprecipitable LDL receptors (Lane C). Even after two hours of incubation with unlabeled methionine, these receptors remained in the

unprocessed precursor form (Lane D). Thus, the patient's fibroblasts contained at least one copy of the mutant allele that produces an abnormal precursor that is not transported to the Golgi apparatus for carbohydrate processing.

To identify the origin of this mutant allele, we performed pulse–chase experiments in cells from both parents. As shown in Figure 2, all the receptors produced by the mother's cells were in the mature form, indicating that they were all produced by her single normal receptor gene. The father's cells exhibited two populations of LDL receptors after a two-hour chase period — one population of normal mature receptors and a second population of abnormal precursor receptors that were not processed. All the receptors produced by the patient's cells remained in the nonprocessed precursor form. These data suggested that the mother had one copy of a normal allele and one copy of a null allele that did not produce immunoprecipitable LDL receptors. The father had one copy of the normal allele and one copy of the mutant allele that produced a nonprocessed receptor. The patient had inherited the null allele from the mother and the allele that produced nonprocessed receptors from the father.

Before transplantation of the liver and heart, the patient was given a tracer dose of ^{125}I-LDL intravenously, and blood samples were collected thereafter for measurement of radioactivity (Fig. 3). The ^{125}I-LDL left her circulation extremely slowly; after 10 days, 30 per cent of the injected ^{125}I-LDL remained. (In normal subjects, less than 5 per cent of radioactivity remains in the plasma at this time.[2,22]) After transplantation, when the patient had been fully ambulatory for several months, the study of ^{125}I-LDL turnover was repeated. At that time the ^{125}I-LDL was removed much more rapidly from the circulation; after 10 days, only 5 per cent of the ^{125}I-LDL remained in the plasma.

The turnover data in Figure 3 were analyzed by the two-pool model of Matthews, [19,22] and the indexes are shown in Table 3. After transplantation, the patient had a decline in the level of total plasma cholesterol, from 1079 to 302 mg per deciliter (27.9 to 7.81 mmol per liter). Her plasma LDL-cholesterol concentration declined from 988 to 184 mg per deciliter (25.5 to 4.76 mmol per liter). The fractional catabolic rate for plasma ^{125}I-LDL is an accurate index of functional LDL-receptor activity in vivo.[11–14] Before transplantation, the patient's fractional catabolic rate was 0.12 pools per day, which is equal to that attributable to clearance of LDL by nonreceptor pathways [11,18]; in other words, there was no detectable expression of the receptor pathway in vivo. After transplantation, the fractional catabolic rate increased to 0.31 pools per day. The normal value (mean ±S.D.) for 16 young adults was 0.43±0.06 pools per day.[11]

On the basis of the measured rate of catabolism of ^{125}I-LDL and the measured pool size of LDL, the production rate of LDL apoprotein (apo-LDL) can be estimated. Although these calculations have limitations,[23] they suggest that before transplantation the patient produced 36 mg of apo-LDL per kilogram of body weight per day, which is four times higher than normal (Table 3). After transplantation the calculated apo-LDL production rate declined to 16.7 mg per kilogram per day, which is still above normal. The normal value (mean ±S.D.) for 16 young adults was 8.5± 1.4 mg per kilogram per day.[11]

Discussion

The data in this paper demonstrate that our patient with the clinical syndrome of homozygous familial hypercholesterolemia actually had a compound genetic disorder. From her mother, she inherited a null allele that failed to produce immunologically or functionally active LDL receptors. From her father, she inherited an allele that produced a mutant receptor that could not be processed to the mature form and thus could not be brought to the cell surface, even though it was capable of recognition by a monoclonal antibody directed against the receptor.

Because of the grim clinical outlook for this patient, she underwent a combined heart–liver transplantation. [16] The liver transplantation was designed to provide her with an organ that produced normal LDL receptors, in the hope that the new receptors would remove LDL from the circulation with normal efficiency. The heart transplantation was necessitated because of the severe myocardial and valvular damage and because the presence of an artificial valve would have been a contraindication to immunosuppressive therapy after liver transplantation. [16] The patient tolerated these operations remarkably well, and her postoperative course has been uneventful up to the present.

After transplantation, the plasma LDL-cholesterol level in Patient FH 728 declined by 81 per cent. Studies of ^{125}I-LDL catabolism indicated that the fractional catabolic rate for LDL increased by 2.5-fold, reaching about 67 per cent of the normal value. This finding is consistent with the observation in animals that the liver accounts for about 75 per cent of the total expression of LDL receptors in vivo. [12–15] Presumably, the LDL level in our patient would be reduced even further if LDL receptors on extrahepatic tissues could be restored. Although the transplanted heart also had normal LDL receptors, the contribution of this organ to removal of LDL from plasma is negligible. [12–14]

In agreement with previous studies in homozygous familial hypercholesterolemia,[18,22,24] the apparent rate of LDL production in our patient was increased markedly before transplantation. This finding can be explained, at least partly, by a lack of receptor-mediated uptake of intermediate-density lipoproteins in the liver, as determined from studies of Watanabe heritable hyperlipidemic (WHHL) rabbits, an animal counterpart of familial hypercholesterolemia. [1] Intermediate-density lipoproteins are derived from very-low-density lipoproteins during the transport of triglycerides in plasma. Normally, about half the intermediate-density lipoproteins are removed from the circulation by binding to LDL receptors in the liver. In homozygous familial hypercholesterolemia, the intermediate-density lipoproteins cannot enter the liver normally, owing to the deficiency of LDL receptors. As a result, these lipoproteins remain in plasma, where they are eventually converted to LDL, thus contributing to overproduction of LDL. [1,23]

The elevated rate of LDL production in our patient was decreased after transplantation, suggesting that the new liver was removing intermediate-density lipoproteins from the circulation at an accelerated rate. However, the precise magnitude of LDL production cannot be estimated accurately from our kinetic studies because the calculations assume that plasma LDL is a homogeneous pool and that all of it is catabolized at the same rate as the ^{125}I-LDL that was injected. Since this assumption is probably not correct,[23] the calculations for the LDL production rate in Table 3 should be interpreted with some caution. Nevertheless, the fall in the apparent production rate, as calculated from the above model, is consistent with the notion that the transplanted hepatic LDL receptors have an important role in regulating the input of LDL as well as in promoting its removal.[1]

We considered the possibility that the enhanced catabolism of LDL seen postoperatively in Patient FH 728 was not due to the functioning of the normal liver but to some unanticipated effect of the operation or of the postoperative drug regimen. Against this thesis is the observation that in seven other patients (ages, 2 to 12) who underwent liver transplantation for a variety of reasons other than familial hypercholesterolemia and who were maintained on a similar drug regimen of prednisone and cyclosporine, the plasma cholesterol level postoperatively was not lowered below normal. The mean total cholesterol level in these seven patients after liver transplantation was 190 mg per deciliter (4.9 mmol per liter), the mean LDL-cholesterol level was 123 mg per deciliter (3.18 mmol per liter), and the mean triglyceride level was 353 mg per deciliter (3.99 mmol per liter).

Although liver transplantation as a method of lowering cholesterol is applicable only to the rare patients with receptor-negative homozygous familial hypercholesterolemia, less drastic treatments that increase the amount of hepatic LDL receptors may have more widespread use in the more common types of hypercholesterolemia. [25] Patients who have one or two copies of the normal LDL-receptor gene can respond to agents that stimulate the normal gene to produce more LDL receptors. [10,11,25] These agents include bile acid-binding resins, such as cholestyramine, and operations, such as ileal bypass, that stimulate the production of LDL receptors by enhancing the liver's demand for cholesterol. [26,27] Newer agents, such as the cholesterol-synthesis inhibitors compactin and mevinolin, also stimulate the production of LDL receptors by inhibiting the liver's cholesterol synthesis and forcing the organ to rely on LDL receptors for an increased proportion of its cholesterol supply. [11,27] These treatments will lower LDL-cholesterol levels in patients with heterozygous familial hypercholesterolemia and in patients with two normal receptor genes whose receptor production has been suppressed by diet and other environmental factors.

Some homozygotes with familial hypercholesterolemia have an incomplete defect and express 5 to 25 per cent of the normal amount of LDL-receptor activity.[2] These patients retain a limited potential to respond to receptor-enhancing agents.[2] However, receptor-negative homozygotes, such as Patient FH 728, who lack the genetic information to produce any functional LDL receptors, cannot respond to these treatments.[2] The only effective therapies for this latter group are the performance of biweekly plasmaphereses[28] and the performance of a portacaval shunt. [18,29] The latter operation reduces LDL levels by up to 50 per cent by diminishing the rate of production of LDL. [18] Liver transplantation should be considered only for the group of homozygotes with familial hypercholesterolemia who are unable to produce any functional LDL receptors and do not respond to other forms of therapy.

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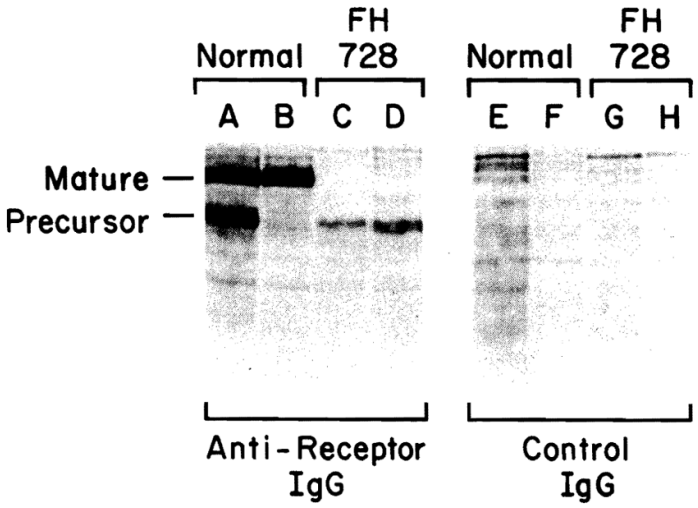

Figure 1.

Kinetics of Processing of LDL Receptors in Fibroblasts from a Normal Subject and Patient FH 728.

Cells were incubated in methionine-free medium containing [^{35}S]methionine for one hour. The medium was then switched to complete medium containing unlabeled methionine for either 15 minutes (A, C, E, and G) or two hours (B, D, F, and H), after which the cells were dissolved in detergents and LDL receptors were immunoprecipitated with monoclonal antireceptor IgG-C7 (A to D). Control precipitations were performed with control monoclonal IgG-2001 (E to H). The immunoprecipitates were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis and fluorography. The positions of migration of the unprocessed precursor receptor (120,000 daltons) and the processed mature receptor (160,000 daltons) are indicated.

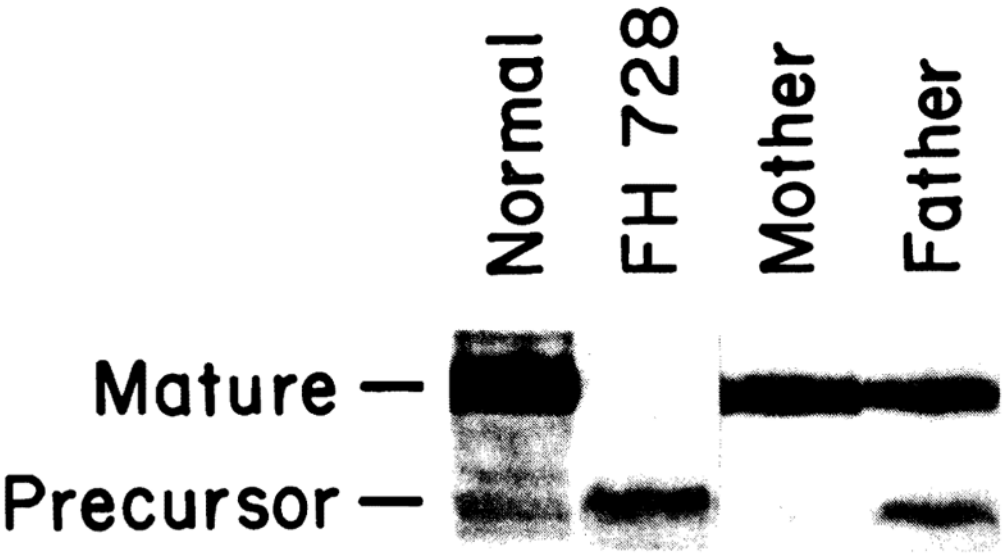

Figure 2.
Electrophoresis of ^{35}S-Labeled LDL Receptors from Patient FH 728 and Her Heterozygous Parents.
Fibroblasts from the indicated subject were incubated in methionine-free medium containing [^{35}S]methionine for two hours (pulse). The medium was then switched to complete medium for two hours (chase), after which LDL receptors were immunoprecipitated and processed for sodium dodecyl sulfate polyacrylamide gel electrophoresis and fluorography. The positions of migration of the unprocessed precursor receptor (120,000 daltons) and the processed mature receptor (160,000 daltons) are indicated.

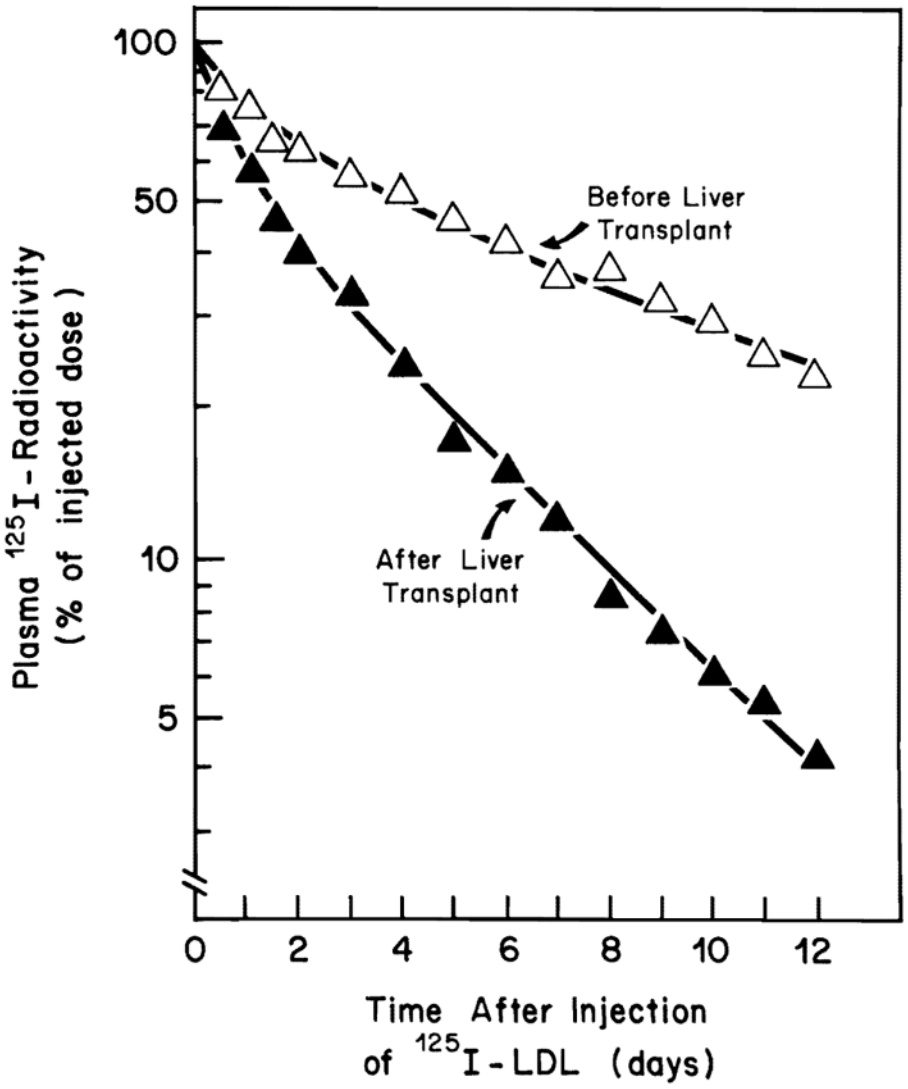

Figure 3.
Plasma Decay Curves after Intravenous Injection of ^{125}I-LDL in the Patient before and after Liver–Heart Transplantation.

Table 1

Metabolism of ^{125}I-LDL by Fibroblasts from the Patient and from the Donor of the Liver and Heart.*

Subject	Surface-Bound ^{125}I-LDL	Internalized ^{125}I-LDL	Degraded ^{125}I-LDL
		ng/mg of protein	
Experiment A			
Normal	152	691	4740
Patient	8.0	17	97
Experiment B			
Normal	191	789	4185
Donor	222	520	4444

*Each monolayer was treated with 2 ml of medium containing 5 per cent lipoprotein-deficient serum and 10 μg of protein per milliliter of ^{125}I-LDL (140 to 180 cpm per nanogram of protein) in the absence or presence of 500 μg of protein per milliliter of unlabeled LDL. After incubation for five hours at 37°C, the total amounts of surface-bound, internalized, and degraded ^{125}I-LDL were determined. The data represent high-affinity values, which were determined by subtracting the values for ^{125}I-LDL in the presence of unlabeled LDL (nonspecific values) from the values in its absence (total values). The nonspecific values comprised <10 per cent of the total values. Each value represents the mean of triplicate incubations.

Table 2

Incorporation of [^{14}C]Oleate into Cholesteryl Esters by Fibroblasts from the Patient and Her Heterozygous Parents.*

Subject	Cholesteryl [^{14}C]Oleate Formed			
	NO ADDITIONS	PLUS 200 μg/ml OF LDL	5 μg/ml OF 25-HYDROXYCHOLESTEROL	LDL:25-HYDROXYCHOLESTEROl RATIO
	(a)	*(b)*	*(c)*	*(b – a)/(c – a)*
	pmol/hr per/mg of protein			
Experiment A				
Normal	198	8800	3000	3.1
Patient	45	33	2610	0.0
Experiment B				
Normal	65	5793	2008	2.9
Patient’s mother	40	3841	2950	1.3
Experiment C				
Normal	235	5210	2330	2.4
Patient’s father	28	1126	916	1.2

*Each monolayer was treated with 2 ml of medium containing 5 per cent lipoprotein-deficient serum supplemented with nothing, LDL, or 25-hydroxycholesterol as indicated. After incubation for five hours at 37°C, each monolayer was incubated for two hours with 0.1 mM [^{14}C]oleate–albumin (9580 to 11,820 dpm per nanomole), after which the cells were harvested for measurement of cholesterol [^{14}C]oleate content. Each value represents the mean of triplicate incubations.

Table 3

Clinical Data and Kinetic Indexes for LDL-Turnover Studies in the Patient before and after Liver–Heart Transplantation.

	^{125}I-LDL Turnover Study	
Index	**BEFORE TRANSPLANTATION**	**AFTER TRANSPLANTATION**
Weight (kg)	20.4	21.1
Height (cm)	112	114
Plasma cholesterol (mg/dl)*		
Total	1079±31	302±32
LDL	988±14	184±23
HDL	35±3	41±2
Plasma triglyceride (mg/dl)*	238±76	218±47
Plasma volume (ml)†	919	955
Plasma LDL protein (mg/dl)*	673	119
Half-time for exponential decay (days)‡		
1st exponential	0.60	0.75
2nd exponential	7.52	3.15
FCR (pools/day)§	0.12	0.31
Apo-LDL production and catabolism		
mg/day	743	353
mg/kg/day	36.4	16.7
Apo-LDL distribution¶	77%	76%

*Mean of six separate measurements made during the course of each turnover study. Plus–minus values are S.D. To convert values for cholesterol and triglyceride to millimoles per liter, multiply by 0.02586 and 0.01129. respectively.

†Estimated as 4.5 per cent of body weight.

‡Half-times of the first and second exponentials of the plasma decay curve.

§Fraction of the intravascular apo-LDL pool catabolized each day, calculated from the two exponentials of the plasma decay curve.

¶Percentage of total body apo-LDL contained in the intravascular space.