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Selective Removal of Low Density Lipoproteins (LDL) by Precipitation at Low pH: First Clinical Application of the HELP System

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Summary. The first clinical application of a new extracorporeal procedure (HELP) for the selective elimination of low-density lipoproteins by heparin precipitation at acid pH is described. Plasma, obtained by filtration of whole blood through a 0.2 μ filter, is continuously mixed with an equal volume of an acetate buffer (pH 4.85) containing heparin. After removal of the precipitated heparin complex by filtration, excess heparin is adsorbed to a specially developed filter and the clear plasma filtrate is subject to bicarbonate dialysis/ultrafiltration to restore physiologic pH and remove excess fluid. The calculated efficiency for the elimination of low-density lipoproteins from plasma by HELP is 100% and is therefore comparable to conventional plasmapheresis. The HELP system shows a high degree of specificity with over 80% of total protein being returned to the patient. Over 130 treatment procedures have now been performed. Patient compliance and acceptance have been excellent and no major complications have been observed.

Key words: Hypercholesterolemia – Low-density lipoproteins – Heparin precipitation – Extracorporeal plasma treatment

Familial hypercholesterolemia is inherited as an autosomal dominant disease. The extensive studies by Goldstein and Brown and their colleagues [6] have revealed that this disorder is caused by mutations in the gene encoding the low-density lipoprotein (LDL) receptor. In its rare homozygous form (1:1,000,000) subjects acquire a defective gene from both parents resulting in a complete absence or a severe diminution of LDL-receptor activity (<20% of normal). Cholesterol levels are massively elevated due to the accumulation of LDL cholesterol in plasma and frequently reach values of 1,000 mg/dl or more. Severe atherosclerosis generally develops in childhood and death from myocardial infarction invariably occurs before the age of 30 [6]. In its heterozygous form (1:500), subjects only have one deficient gene and total LDL-receptor activity is approximately 50% of normal. Cholesterol levels are in the range of 300–500 mg/dl and coronary artery disease usually occurs in the fourth or fifth decade of life.

Treatment of the homozygous form of familial hypercholesterolemia by diet and drug therapy alone is ineffective. Encouraging results have, however, been obtained in the treatment of this disorder by plasma exchange. In five homozygotes treated with regular plasmapheresis for a mean of 8 years an improved survival was observed, compared with their untreated siblings [17]. At present, plasma exchange would appear to be the most effective mode of therapy for this particular form of the disorder. The use of plasmapheresis for the treatment of the heterozygous form of familial hypercholesterolemia is less equivocal. Thompson reported that plasmapheresis brought symptomatic benefit to three out of four heterozygotes [14], whereas Simons et al. [12] concluded that plasmapheresis offered no further advantages over conventional therapy. However, as pointed out by Thompson and Myant [16], plasmapheresis was only performed every 4 weeks in the latter study [12] as opposed to 1–2 weeks in the former [14].

Conventional plasmapheresis therapy has involved replacement of the patient's plasma with

Abbreviations: AT III = Antithrombin III; HDL = High density lipoproteins; HELP = Heparin extracorporeal LDL precipitation; LDL = Low density lipoproteins; VLDL = Very low density lipoproteins

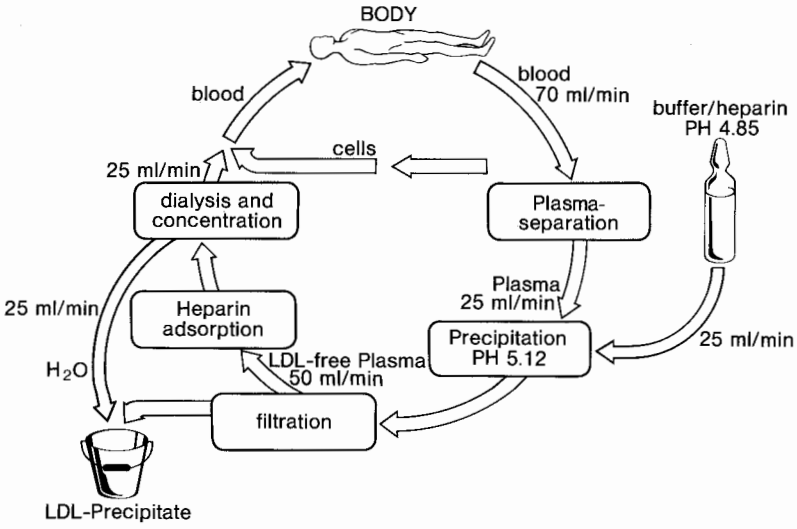

Fig. 1. Schematic representation of the HELP system

a donor plasma (fresh frozen plasma) or more usually a plasma protein fraction with attendant complications due to the introduction of foreign proteins and transmission of infectious diseases. Ways have therefore been sought to selectively remove LDL from plasma followed by the return of the patient's own plasma. The first reports of such a procedure involved the adsorption of LDL to heparin-agarose beads [8] or with the aid of immobilized antibodies [7, 13]. Other methods for the removal of LDL involve cascade filtration [3, 23], adsorption to immobilized dextran sulfate [23], and thermofiltration [9].

We now describe the first clinical application of a procedure for the continuous elimination of LDL from plasma based on LDL precipitation at low pH in the presence of heparin [2, 5, 10, 11, 21]. This procedure has been termed HELP: heparin extracorporal LDL precipitation.

Materials and Methods

Procedure for HELP

The apparatus necessary for the continuous elimination of LDL from plasma by HELP has been developed in collaboration of the Department of Clinical Chemistry, University of Göttingen with B. Braun Melsungen, (Melsungen, FRG). The flow diagram for this procedure is illustrated in Fig. 1. A 0.2-μ plasma filter is used to separate plasma from whole blood (filtration 1) at blood flow rates of 60–80 ml/min. The plasma is then mixed continuously with an equal volume of an acetate buffer, pH 4.85 containing 100 U/ml heparin (Braun). The flow rates of plasma and buffer are identical and generally range from 20–25 ml/min (depending on blood flow rate and efficiency of the plasma filter). Mixing occurs in a precipitation chamber and the suspension is recirculated through a 0.4-μ polycarbonate membrane filter (filtration 2). An LDL-free filtrate is obtained from this filter which is then passed through a heparin adsorber to remove excess heparin. This adsorber is capable of completely absorbing the excess heparin at a pH of 5.12 without affecting total plasma protein [5]. After passage through this adsorber, the plasma buffer mixture with a pH of 5.12 is subject to bicarbonate dialysis/ultrafiltration to restore physiologic pH and to remove excess acetate and fluid [2]. Finally, the LDL-free plasma is mixed with the blood cells from the plasma filter before being returned to the patient.

The various parts (tubing, filters, etc.) required for this procedure are all sterile, disposable systems intended for single use only. The total extracorporeal volume is approximately 1,300 ml of which at least 50% is buffer during treatment. If necessary the relative amount of buffer to plasma can be increased in order to reduce the volume of plasma in the extracorporeal system. The heparin concentration can then be reduced accordingly and the excess fluid is removed by ultrafiltration through the dialysis filter. The system is initially primed and washed with a sterile isotonic NaCl solution prior to use.

Volunteers and Patients

Informed written consent was obtained from all volunteers and patients. After extensive investigations in animals [2, 5], the first human trials with

HELP were performed on six healthy male volunteers. Each volunteer underwent a single treatment of either 2 l ($n=4$) or 3 l ($n=2$) of plasma. After the successful conclusion of these trials and the consent of the university ethics committee, the first clinical trials were initiated. This report covers the data of three severely hypercholesterolemic patients who because of inadequate response to diet and drug therapy are now being treated by HELP.

Patient 1 (RK) was 46-year-old male with a family history of coronary heart disease. He suffered his first myocardial infarction at the age of 39. Hypercholesterolemia was detected and the patient was put on diet and drug therapy. A second myocardial infarction complicated by aneurysma of the anterior wall occurred at the age of 42. Angiography of the coronary arteries revealed severe three-vessel disease and in October 1982 a triple aorta coronary bypass and resection of the aneurysmic aorta was diagnosed and operated. In 1985 he was referred to our clinic with a cholesterol level of 350 mg/dl despite diet and cholestyramine treatment (3×6 g/day). At this time he suffered from angina pectoris when cold or during strenous exercise.

Patient 2 (HE) was 31-year-old male with a family history of type II hypercholesterolemia and coronary heart disease. Untreated LDL-cholesterol levels ranged from 400–500 mg/dl. Dietary advice and treatment with cholestyramine produced only a slight reduction in these levels.

Patient 3 (ES) was 44-year-old female with type II hypercholesterolemia. Untreated LDL-cholesterol levels were in the range 300–350 mg/dl. Dietary and drug treatment only lowered these levels to around 270–290 mg/dl. ES suffers from left thoracic pain and has electrocardiographic evidence of coronary heart disease.

Anticoagulation for HELP therapy was performed using heparin (Braun, Melsungen) as described for standard hemodialysis [18]. Patients received an initial dose of 35 U/kg body weight and a continuous infusion of 1,000 U/h during extracorporeal Treatment. Infusion was normally stopped approximately 30 min before the end of treatment.

In two patients (RK and ES) with small superficial veins a Cimino-Bresica side-to-side anastomosis between the art. radialis and vena cubitalis was performed in order to obtain adequate blood flow rates. Treatment normally lasted from 2–3 h depending upon the volume of plasma treated (2 or 3 l).

Laboratory Measurements

The various clinical chemical, hematological, and coagulation parameters were measured using standard techniques subject to a stringent quality control in the Department of Clinical Chemistry of the University Clinic, Göttingen. Immunoglobulins and complement factors were determined in the Serology Laboratory, University Clinic, Göttingen. Concentrations of the different lipoprotein classes were determined by either quantitative lipoprotein electrophoresis [22] or precipitation techniques [1] for LDL cholesterol (Quantolip-LDL, Immuno, Heidelberg) and HDL cholesterol (Boehringer, Mannheim). Lp(a) concentrations were measured by radial immunodiffusion (Combi RID, Immuno Diagnostica, Heidelberg).

Results

Efficiency and Specificity of the LDL Elimination

In conventional plasmapheresis, in which patient's plasma is continuously replaced by a cholesterol-free plasma protein fraction, the final LDL-cholesterol concentration at the end of plasmapheresis can be predicted from Eq. (1) [15]:

$$\frac{CE}{CO} = e\frac{-PE}{PV} \tag{1}$$

where CE is the LDL-cholesterol concentration at the end of plasmapheresis, CO is the LDL-cholesterol concentration prior to plasmapheresis, PE is the volume of plasma exchanged, and PV is the plasma volume of the patient. For example, when $PE/PV=1$ (i.e., the plasma volume exchanged equals the plasma volume of the patient), the final LDL-cholesterol concentration will be 37% of the initial level.

If a complete elimination of LDL-cholesterol does not occur, then Eq. (1) will have the form:

$$\frac{CE}{CO} = e\frac{-kPE}{PV} \tag{2}$$

where k is a factor of less than 1, reflecting the efficiency of the elimination of LDL. For example, if only 50% of the plasma LDL is removed by the system (i.e., $k=0.5$), then the LDL concentration after the exchange of a volume of plasma (PE) equal to the plasma volume of the patient (PV) will be 61% of the initial LDL concentration.

Knowing CE, CO, PE, and PV, k can be derived for any lipoprotein or protein present in plas-

Table 1. Efficiency of the elimination of various plasma lipoproteins and proteins through HELP

	k[a] (mean ± SD)
LDL-cholesterol	1.02 ± 0.13
Beta-lp-cholesterol	0.92 ± 0.18
Fibrinogen	0.97 ± 0.15
C-4 complement	0.97 ± 0.24
Plasminogen	0.84 ± 0.16
C-1 inhibitor	0.82 ± 0.18
C-3 complement	0.59 ± 0.19
AT III	0.44 ± 0.13
Total protein	0.22 ± 0.09
HDL/alpha-cholesterol, albumin, IgG, IgA, IgM, transferrin, ferritin	< 0.18

[a] Derived as described in Results, k is the mean from 20 different HELP procedures

ma and this factor then defines the efficiency and specificity of the elimination procedure.

In vitro experiments (Armstrong, Noll, and Seidel, unpublished observations) have revealed that in addition to LDL, a limited number of other plasma proteins are coprecipitated by heparin at acidic pH. The major proteins involved are fibrinogen, plasminogen, C-4 complement, C-1 inhibitor, and to a lesser extent, C-3 complement. A small amount of AT III is also precipitated. We, therefore, calculated the mean k values from a total of 20 HELP procedures for these and numerous other plasma proteins (Table 1). A complete elimination of LDL cholesterol, beta-lp-cholesterol, fibrinogen, and C-4 complement occurs during HELP. Plasminogen and C-1 inhibitor are also precipitated to a large extent, whereas only a limited elimination of C-3 complement and AT III occurs. A small loss of total protein is observed due to the precipitation of the above proteins and presumably also due to unspecific losses in the extracorporal system. Of the other proteins and lipoproteins that were measured, only a minor, unspecific elimination was observed.

The acute effect of HELP on the plasma levels of these different lipoproteins and proteins is illustrated in Table 2. The mean plasma levels were calculated from 25 different HELP treatments both before (SP) and at the end (EP) of each treatment. In the case of proteins that are not specifically precipitated by heparin at low pH, plasma concentrations at the end of HELP were generally in the range of 80%–90% of the initial value. Samples taken 24 h after the end of treatment showed that these proteins had retained their original level. AT III was only reduced to 75% of its original

Table 2. Acute effect of HELP on various plasma lipoproteins and proteins

Lipoprotein/protein	Mean[a]		EP/SP × 100 (%)
	SP[b]	EP[c]	
Total cholesterol (mg/dl)	327	177	54
Total triglyceride (mg/dl)	207	124	60
Beta-lp-cholesterol (mg/dl)	235	116	49
LDL-cholesterol (mg/dl)	245	111	45
Pre-beta-lp-cholesterol (mg/dl)	35	12	34
Alpha-lp-cholesterol (mg/dl)	56	50	89
HDL-cholesterol (mg/dl)	51	43	84
Lp(a) (mg/dl)	59	32	54
Fibrinogen (mg/dl)	320	157	49
Plasminogen (mg/dl)	5.8	3.0	52
AT III (%)	91.4	68.4	75
Total protein (g/dl)	6.4	5.4	84
Albumin (g/dl)	4.3	3.7	86
IgG (mg/ml)	9.3	7.8	84
IgA (mg/ml)	2.4	2.0	83
IgM (mg/ml)	1.5	1.2	80
Transferrin (mg/dl)	313	270	86
Ferritin (μg/dl)	93	86	93
C-3 complement (mg/dl)	106	65	61
C-4 complement (mg/dl)	33.2	16.4	49
C-1 inhibitor (%)	35.7	17.9	50

[a] Means were derived from a total of 25 HELP treatments
[b] Value before the start of HELP
[c] Value at the end of HELP

level and it too had recovered within 24 h. Of the proteins that are specifically precipitated by heparin at acidic pH, C-3 complement was lowered to 61% of its initial value, whereas LDL cholesterol, fibrinogen, plasminogen, C-4 complement, and C-1 inhibitor were all reduced to levels ranging from 45%–55% of the original value. The lowest level was observed with LDL cholesterol. Lipoprotein (a) is also virtually quantitatively eliminated.

Interpretation of the data for total triglycerides and pre-beta-lp-cholesterol is difficult. The heparinization of the patients that is necessary for extracorporeal treatment will lead to increased lipolysis of triglycerides due to the release and activation of lipoprotein lipase. It is therefore not possible to determine to what extent the reduction in these parameters is due to precipitation and/or lipolysis.

Acute Effect of HELP on Various Clinical Chemical, Hematological, and Hemostasiological Parameters

Plasma electrolyte concentrations were unaffected by HELP (Table 3). Various plasma enzyme activities also showed no marked changes due to this treatment procedure, indicating that neither pre-

Table 3. Acute effect of HELP on various clinical chemical, hematological, and coagulation parameters

Parameter	Mean[a]		SP/EP ×100 (%)
	SP[b]	EP[c]	
Sodium (mmol/l)	139	139	100
Potassium (mmol/l)	4.0	4.3	107.5
Calcium (mg/dl)	8.9	8.8	99
Inorganic phosphate (mg/dl)	3.5	3.4	97
Chloride (mmol/l)	106	109	103
Iron (μg/dl)	93	81	87
GOT (U/L)	9.8	9.0	92
GPT (U/L)	10.8	9.5	88
GGT (U/L)	120.0	103.0	86
AP (U/L)	20.7	16.8	81
CK (U/L)	37.1	25.1	68
LDH (U/L)	140	137	98
Amylase (U/L)	20.1	17.4	87
Glucose (mg/dl)	92	87	95
Urea-N (mg/dl)	13.6	12.5	92
Creatinine (mg/dl)	0.8	0.7	88
Uric acid (mg/dl)	4.1	4.1	100
Total bilirubin (mg/dl)	0.33	0.45	136

[a] Means were derived from a total of 25 HELP treatments
[b] Value before the start of HELP
[c] Value at the end of HELP

Table 4. Acute effect of HELP on coagulation and hematological parameters

Parameter	Mean[a]		SP/EP ×100
	SP[b]	EP[c]	
Quick (%)	85	47	55
Thrombin time (s)	14.5	29.9	–
Partial thromboplastin Time (s)	37.6	70.6	–
Heparin (U/ml)	0	0.17	–
Hemoglobin (g/dl)	13.8	13.3	96
Hematocrit (%)	40.5	39.3	97
Erythrocytes (Mio/μl)	4.31	4.14	96
Leukocytes (×1,000/μl)	6.3	7.1	113
Thrombocytes (×1,000/μl)	241	221	92

[a] Means were derived from a total of 25 HELP treatments
[b] Value before the start of HELP
[c] Value at the end of HELP

cipitation of these enzymes had occurred nor had a loss of enzyme activity at the low pH required for the precipitation. Other clinical chemical parameters were also unaffected by HELP.

Of particular importance was the influence of HELP on hemostasis. As can be seen from Table 4, thrombin time and partial thromboplastin times were increased at the end of a HELP procedure and the Quick values were correspondingly reduced. The values observed, however, are typical for such extracorporeal treatment procedures in which heparinization of the blood is necessary [18]. Heparin levels at the end of treatment were not excessively elevated, indicating that the large amounts of heparin necessary for the effective precipitation of LDL had been completely removed by the heparin adsorber [5]. This was confirmed from samples taken from the extracorporeal system after the heparin adsorber at the end of treatment. No heparin could be detected. Finally, HELP was found to have no influence on hematological parameters (Table 4).

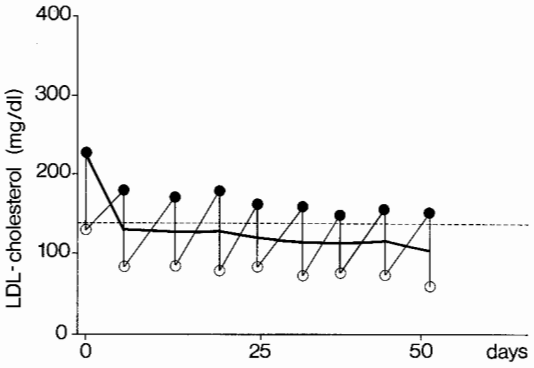

Fig. 2. Effect of HELP treatment on serum LDL-cholesterol concentrations in patient 1. The *closed circles* ● represent the LDL-cholesterol concentrations prior to a HELP procedure and the *open circles* ○ the levels directly after HELP; —— mean LDL-cholesterol concentrations during HELP treatment; –– 140 mg/dl LDL-cholesterol

HELP had no effect on the pH of venous blood in our patients, the mean values being 7.357 ($n=25$) at the start of treatment as compared with 7.363 ($n=25$) at the end of treatment.

Long-Term Treatment with HELP

To date, our three patients have been treated with a total of 9, 16, and 20 HELP procedures over periods of 8, 23, and 24 weeks, respectively. The LDL-cholesterol levels for patients 1 and 3 during treatment are shown in Figs. 2 and 3. Prior to being referred to us patient 1 (Fig. 2) had total cholesterol levels in the range of 350–400 mg/dl. When we first saw him his LDL-cholesterol concentration was 275 mg/dl. Through appropriate medication and diet it was possible to reduce this value by approximately 17%–229 mg/dl. Regular HELP treatment caused a further significant reduction in his mean LDL cholesterol. Posttreatment LDL-cholesterol concentrations were in the range of 70–80 mg/dl. The mean LDL-cholesterol concentration to which the arterial wall is exposed will

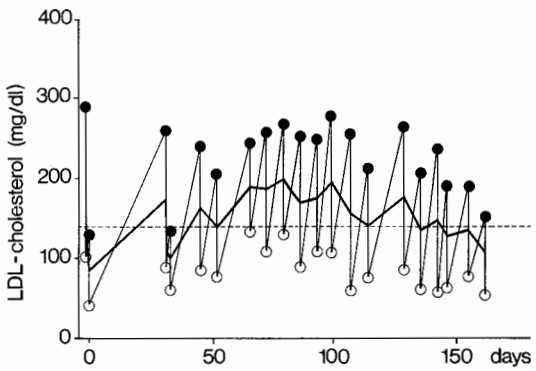

Fig. 3. Effect of HELP treatment on serum LDL-cholesterol concentrations in patient 2. See legend to Fig. 2 for explanation of symbols

depend on the form of the rebound curve [14]. For the sake of convenience we have simply calculated the mean LDL concentrations between treatments as the sum of the former posttreatment value and the following pretreatment value divided by two. Although this will underestimate the true mean LDL-cholesterol concentration, it serves to assess the effectiveness of treatment provided that this is performed on a regular basis. In the case of patient 1 it can be seen that HELP treatment had led to a considerable reduction (50%) in his mean LDL-cholesterol concentrations, to levels lower than those of age-matched healthy controls.

The serum LDL-cholesterol concentrations of patient 3 (Fig. 3) had ranged between 270 and 290 mg/dl despite diet and medication prior to treatment by HELP. After an initial period of irregular treatment, it was possible to reduce her mean LDL-cholesterol concentrations to 40% of the starting concentration and to values lower than 140 mg/dl. The greatest effect in this patient was observed when HELP was combined with a combination of fenofibrate and sitosterin, but not with cholestyramine.

Patient 2, the youngest patient, had the most severe hypercholesterolemia of the three. His LDL-cholesterol concentrations were in the range of 350–400 mg/dl before starting HELP, despite dietary advice and medication. Due to his profession he has not been able to perform HELP on a regular basis. Thus, although his LDL-cholesterol levels were considerably reduced at each treatment procedure (<40% of the starting concentration) the time intervals between procedures were such that his LDL-cholesterol concentrations often retained their original pretreatment values.

We have also carefully monitored those plasma proteins that are coprecipitated with LDL during HELP. Despite the long-term intensive treatment, pretreatment levels of fibrinogen, plasminogen, C-4 complement, C-3 complement, and C-1 esterase inhibitor have remained stable, indicating that treatment does not lead to a deficiency of these proteins.

Clinical Observations

Over 130 treatments have now been performed with the HELP procedure on all our patients ($n=5$). Overall treatment tolerance has been good and no major complications have been observed. Minor complications included hematoma of the venous puncture site ($n=3$), moderate chills and transient shivering ($n=4$), and increased fatigability particularly after a 3-l treatment. No alterations in pulse rate, blood pressure, or body temperature were observed.

Discussion

A procedure to selectively remove LDL from plasma for the treatment of severe familial hypercholesterolemia will have to fulfil certain requirements in order to become established in clinical practice. It must be safe and without risk or discomfort to the patients, handling must be relatively straightforward, and removal of LDL must be effective and specific. The apparatus and systems necessary for treatment will have to be readily available so that the procedure is not restricted to specialist centers. The newly developed HELP system based on the precipitation of LDL with heparin at acidic pH [10, 21] goes a long way to satisfying these requirements. The various filters and tubing systems required are all sterile disposable units intended for single use only, thus minimizing the risk due to infection. The precipitation of LDL from plasma is achieved by the addition of an acetate buffer containing heparin. Both of these substances are not "foreign" to the plasma and so should present no immunological problems during chronic treatment of patients. The excess acetate is effectively removed by dialysis [2] which also restores the physiologic pH of the plasma and the excess heparin is retained by a specially developed adsorber [5]. We have now performed over 130 treatments with HELP without observing any major complications. Patient compliance and acceptance have been good. The treatment with 3 l plasma is completed within 3 h and patients can be treated on an outpatient basis under standardized conditions giving reproducible results with regard to the elimination of LDL.

The calculated efficiency for the elimination of LDL by HELP is 100%; in a single passage through the extracorporeal system LDL are totally removed from the patient's plasma. This procedure is therefore as effective as conventional plasmaphreresis and demonstrates a high reproducibility. In addition to LDL a limited number of other plasma proteins are coprecipitated under these conditions (Armstrong, Noll and Seidel, unpublished observations). It is important to note that fibrinogen is removed as effectively as LDL by HELP. The reduction in mean fibrinogen levels may indeed be very beneficial since it will lower the viscosity of the blood and may therefore improve perfusion of tissues in severe atherosclerotic vascular damage. Furthermore, fibrinogen and in particular its degradation products can both inhibit PGI_2 synthesis by endothelial and vascular smooth muscle cells [20], thereby facilitating platelet aggregation and can also cause injury to endothelial cells [19]. Together with LDL, fibrinogen probably plays an important role in atherogenesis and since it is often elevated in hypercholesterolemia it deserves therapeutic attention.

Thompson has regularly used a plasma protein fraction which does not contain fibrinogen for conventional plasma exchange therapy of familial hypercholesterolemia and demonstrated that fibrinogen levels returned to normal within 1 week. We have observed a similar kinetics in our patients.

We have as yet observed no ill effects due to the coprecipitation of plasminogen and the complement factors C-3, C-4, and C-1-esterase inhibitor. Plasma levels had returned to normal within 1–2 days and even after 24 weeks of regular treatment, pretreatment levels of these proteins were normal. On the basis of our in vitro studies we assume that the acute reduction in the complement factors during HELP is most probably due to coprecipitation with heparin rather than to membrane activation of the complement system as is often seen in extracorporeal treatment procedures. HDL, albumin, and plasma globulin concentrations are practically unaffected by the HELP treatment.

Special attention was focussed on hemostasis in our patients because of the high concentrations of heparin that are needed for LDL precipitation in the extracorporeal system. The heparin adsorber effectively retained the excess heparin and coagulation parameters at the end of plasmapheresis were typical for an extracorporeal treatment procedure due to the continuous heparin infusion necessary to prevent blood coagulation in the extracorporeal system. No bleeding complications were observed. The present HELP procedure is therefore an alternative to conventional plasmapheresis for the treatment of familial hypercholesterolemia. It displays the same efficiency as the conventional method while retaining a high degree of specificity and has the advantage that the patient is not exposed to foreign proteins with their attendant immunological problems. There should also be a lower risk of infection using this treatment procedure. Furthermore, it displays a high degree of reproducibility which will therefore allow a consistent therapy independent of the clinic performing the treatment.

While the extracorporeal removal of LDL appears to be indicated for homozygotous familial hypercholesterolemia [17], it remains to be established whether an intensive LDL-lowering therapy combined with diet and drug therapy can lead to a regression of atherosclerosis in patients with other forms of severe hypercholesterolemia. Our method should in most instances be powerful enough to achieve mean plasma LDL-cholesterol concentrations of 140 mg/dl and less which on the basis of coronary angiography studies [4] are associated with a negligible coronary risk. The mean LDL-cholesterol concentration between two HELP treatments will be dependent on both the maximal efficiency of the system to remove LDL and on the kinetics of the LDL increase following the extracorporeal treatment. It is to be expected that the use of drugs affecting hepatic cholesterol synthesis will help to extend the time intervals between HELP treatments.

We are presently organizing a multicenter study to investigate the effect of such a maximal therapy on hypercholesterolemia using the HELP procedure.

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