



Plaquex®

Plaquex[®] Plaquex[®] Forte

For the treatment of
disorders of lipid
metabolism and of
atherosclerosis

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1. Drug Profile

Plaqueux contains essential phospholipids (EPL), highly purified fraction of soybean phosphatidylcholine. While they correspond to endogenous phosphatidylcholine in their chemical structure, they are distinguished by their very high content of polyunsaturated fatty acids. More than 50 % of the phosphatidylcholine molecules are esterified with linoleic ester in the 1-position and 2-position.

1,2-dilinoleoylphosphatidylcholine therefore, constitutes the main active ingredient of EPL phospholipid fraction.

In the body EPL substitutes endogenous phospholipids supporting the function of the latter:

- After intravenous application of essential phospholipids are incorporated into serum lipoproteins – and into high-density lipoproteins (HDL) in particular – where they contribute to the formation of the surface monolayer. EPL-enriched HDL have an increased capacity for cholesterol uptake from serum (low-density lipoproteins LDL) and tissue. A pathological increase in the LDL cholesterol/HDL cholesterol ratio is clearly reduced.

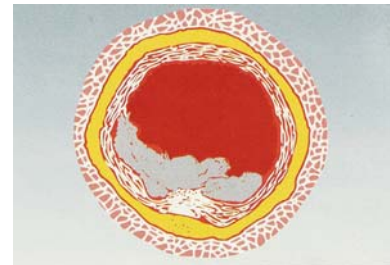


Fig.1 Schematic representation of an atheromatous plaque

- The enzyme lecithin-cholesterol-acyltransferase (LCAT) localised on HDL is phospholipid-dependent. Its activity is intensified by EPL; as a result more cholesterol can be converted into cholesterol linoleic acid esters, thus being readily transportable by the HDL and thereby promoting cholesterol reverse transport from peripheral tissue to the liver. EPL micelles are capable of simulating the transport function of the HDL: they form complexes with the apoprotein A-1 in serum and, therefore, may bind and remove cholesterol from tissue.

- Through activation of phospholipid-dependent lipolytic enzymes (eg. Hepatic triglyceride lipase [HTGL] and lipoprotein lipase [LPL]) EPL promotes the break down of chylomicrons and VLDL particles, which is the precondition for an increased formation of HDL discs. Serum triglyceride levels are reduced.

- Phospholipids in a bilayer arrangement constitute the basic structure of cellular membranes. EPL are incorporated into the membrane fractions of liver cells, for instance, and their organelles, replacing endogenous phospholipids. They improve fluidity and all closely membrane-related processes such as the activity of membrane-bound enzyme systems e.g. in mitochondria and in the endoplasmic reticulum.

- EPL also are incorporated into the membranes of platelets and red blood cells where they normalize the cholesterol/phospholipid ratio (C/P) and hence their fluidity and deformability. The increased tendency of these cells to adhere and aggregate – resulting from an increased accumulation of cholesterol in the membrane and/or oxidized lipids – is reduced by EPL together with blood viscosity. Blood rheology and microcirculation are improved.

- Due to their amphiphilic character, EPL display surfactant, i.e. emulsifying properties that are used for example in the prevention and treatment of fat embolism.

- Investigations into the importance of the highly unsaturated fatty acids contained in EPL as precursors of prostaglandins, as well as the influence of EPL on the properties of LDL-receptors are in progress.

- In animals, evidence for reversal of atherosclerotic changes under EPL was obtained in experimentally induced atherosclerosis. In man, amelioration of atherosclerotic symptoms was observed after long-term treatment with EPL. Moreover, provisional clinical results suggest a possible decrease in the size of atherosclerotic plaques.

- Plaquex, a plant derived drug, is very well tolerated even during long-term treatment. No serious adverse effects have been reported so far.

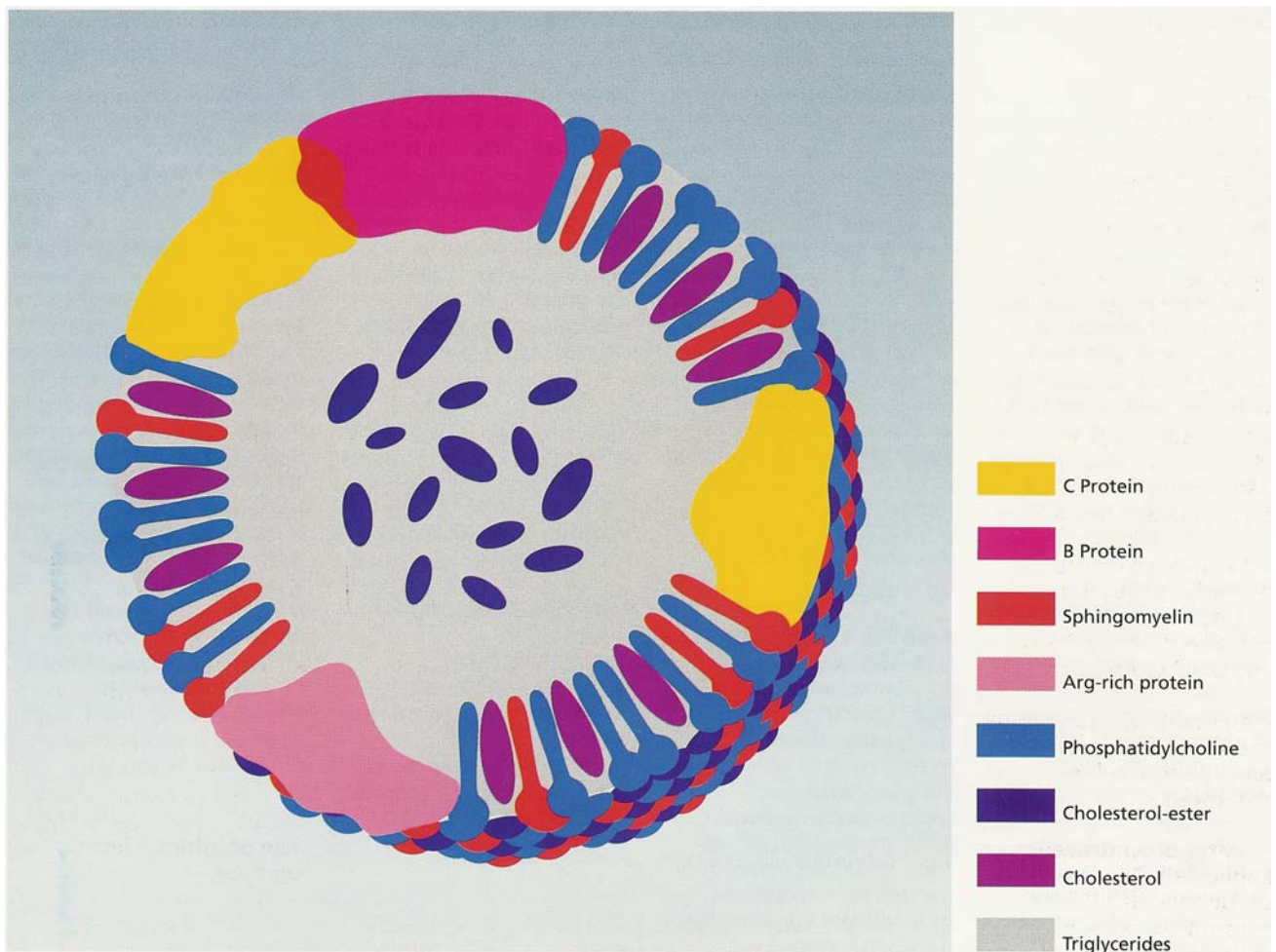


Fig. 2: Cross section of a VLDL (accord. to STEIN, Y., D. STEIN. Atherosclerosis – is it reversible? SCHETTLER, G. et al. (Eds.) Springer: Berlin 1978, 63-73)



2. Basic Information

Composition

Plaquex :

1 vial of 50 ml contains 2500 mg EPL, 10 mg Vitamin E, 1250 Deoxycholic acid, 450 mg Benzylalcohol, 120 mg Ethanol.

Plaquex Forte:

1 vial of 25 ml contains 2500 mg EPL, 10 mg Vitamin E, 1250 Deoxycholic acid, 450 mg Benzylalcohol, 120 mg Ethanol.

Indications

Hyperlipoproteinaemia (hypercholesterolaemia and hypertriglyceridaemia)

Atherosclerosis irrespective of site, e.g.:

Coronary atherosclerosis

Angina pectoris

Condition after myocardial infarction

Impaired cerebral or peripheral circulation

Intermittent claudication

Gangrene

Nephrotic syndrome

Vascular diseases – especially those associated with diabetes mellitus

As presurgical treatment for the prevention of thrombo-embolism

Prevention and treatment of fat embolism

Liver disease

Contraindications

Due to its content of benzylalcohol (stabilizer) the preparation must not be used in new-born or premature babies.

Side-effects

In very rare cases hypersensitivity reactions due to benzylalcohol may occur. If given too fast a rapid decrease of blood pressure may occur. Diarrhea will occur in severely atherosclerotic patients. Rare cases of thrombophlebitis have been reported – mainly due to wrong application or using the wrong catheter material.

Precautions

The treatment protocol must be followed exactly to avoid thrombophlebitis. Only clear solutions are to be used. Plaquex can only be mixed in 5 % dextrose or glucose or laevulose. Nothing else should be mixed with Plaquex.

Dosage and Administration

Plaquex:

Mix Plaquex (room temperature) with 250 ml of D5W (DO NOT USE SALINE/SALT SOLUTION!) The use of D5W in Diabetics is no problem.

Treatment No 1	use	20ml	Plaquex
Treatment No 2	use	30ml	Plaquex
Treatment No 3-20	use	50ml	Plaquex

The infusion must be administered intravenously slowly for the duration of at least 90 minutes. For the infusion we highly recommend the use of an indwelling 22G or 24G Teflon catheter manufactured by Becton Dickinson or Braun. We have noticed that Terumo catheters react with the Plaquex solution and cause Phlebitis, therefore we recommend using the BD catheters. A butterfly can also be used.

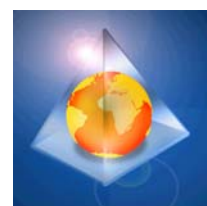
Plaquex Forte:

Mix Plaquex (room temperature) with 250 ml of D5W (DO NOT USE SALINE/SALT SOLUTION!) The use of D5W in Diabetics is no problem.

Treatment No 1	use	10ml	Plaquex
Treatment No 2	use	15ml	Plaquex
Treatment No 3-20	use	25ml	Plaquex

In patients with low body weight and in Asian patients the maximum dosage should not exceed 30 ml Plaquex or 18 ml Plaquex Forte.

Plaquex®



3. Chemistry

Essential phospholipid (EPL) are a highly purified phosphatidylcholine fraction isolated from soy beans. The substance is particularly rich in polyunsaturated fatty acids, with linoleic acid accounting for approx. 70 % and is therefore also termed polyenylphosphatidylcholine (PPC).

Fatty acid	in 1-position %	in 2-position %	total %
C 16 : 0 palmitic acid	24.0	1.7	12.9
C 18 : 0 stearic acid	7.9	1.0	4.4
C 18 : 1 oleic acid	10.9	10.0	10.5
C 18 : 2 linoleic acid	52.4	80.6	66.5
C 18 : 3 linolenic acid	4.7	6.7	5.7

Table 1: Fatty acid composition (mol %) of EPL derived from soybeans, determined after hydrolysis (phospholipase A2), by gas chromatography (LEKIM et al. [37])

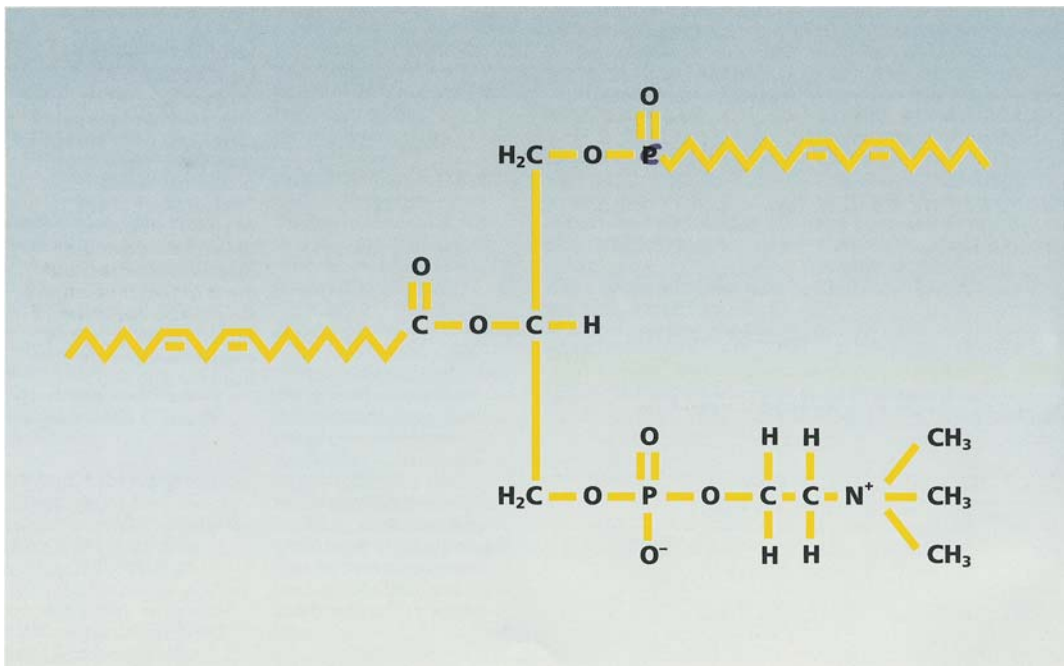


Fig. 3: 1,2-dilinoleoylphosphatidylcholine (LEKIM et al. 37)

More than 50 % of the molecules are phosphatidylcholines that have been linoleic acid bound in positions 1 and 2; i.e. the main active substance is 1,2-dilinoleoylphosphatidylcholine (see fig. 3) which normally does not exist in the human body.

4. Toxicology/Teratology

The following gives a short survey of the most significant studies on the toxicology and teratology of phosphatidylcholine after intravenous application.

4.1 Acute Toxicity

Species	LD ₅₀
Mouse	11.7 ml/kg body weight i.v.
Rat	15.2 ml/kg body weight i.v.
Dog	7.8 ml/kg body weight i.v.

4.2 Subchronic Toxicity

In 3-month screening studies, the “no-effect dose”, in terms of systemic tolerance, was 0.9 ml/kg body weight solution for injections in dogs, and 0.3 ml/kg body weight for rhesus monkeys.

4.3 Screening for Embryotoxic and Teratogenic Effects

The tests which involved Wistar rats and Russian White rabbits were based on the FDA “Guidelines for reproduction studies for safety evaluation of drugs for human use “ (1966) as well as on the WHO “Principles for the testing of drugs for teratogenicity “ 1967.

From their 6th to 15th day of gestation rats were given 1000 mg phosphatidylcholine intravenously. Rabbits received i.v. administrations of 250 to 1000 mg phosphatidylcholine from their 1st to 6th day of gestation. One group each served as controls receiving no treatment.

By the end of the tests no differences could be observed between the dams and the controls, nor did the foetuses show any substance-related changes. On dissecting the young no substance-induced pathological findings were made.

No mutagenic potential was determined for the test compound.

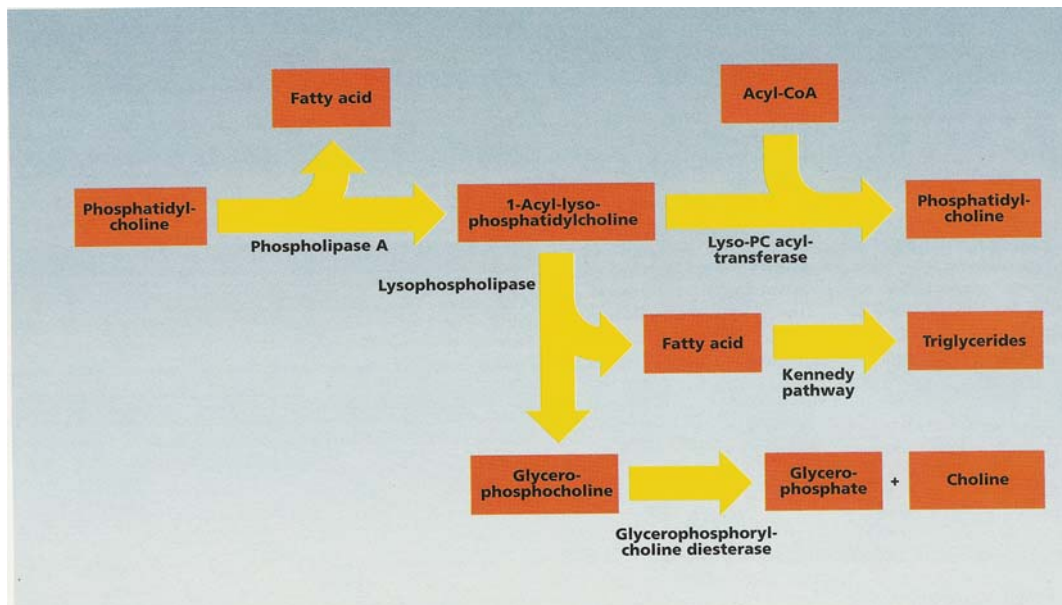
In short, results showed that under the conditions used, the test compound produced no effects on either the pregnant/lactating dams or the perinatal and postnatal development of their young. In other words no indications of an embryotoxic or teratogenic action could be found.

Extensive investigations on acute and chronic toxicity in various species of animals showed very good tolerance of EPL in short-term as well as long-term trials. Investigations of teratogenicity revealed that even high doses of EPL had no toxic effect on dams and foetuses. The good tolerance of Plaquex has been confirmed during many years of clinical use of the preparation.

5. Pharmacokinetics

J. Hölzl (23) carried out experiments in mice and rats with radiolabelled EPL administered intravenously. The mean elimination rates from the plasma after 15 minutes, 75 minutes and 10 h were approx. 80 %, 92 % and 99 % of the administered active principle.

EPL accumulated chiefly in the liver, spleen and lungs and phospholipid fractions of the serum lipoproteins were exchanged for EPL from the serum, As could be demonstrated in animal experiments involving different species, most of the highly unsaturated phosphatidylcholine was incorporated into the HDL fraction (23,52,64,74,76).



6. Experimental Pharmacology of EPL

In animal studies on the pharmacology of EPL, the compound has been administered orally, intravenously, subcutaneously, intracardially or intraperitoneally to evaluate its effect on lipid metabolism disorders prophylactically, therapeutically or with concurrent treatment.

Experimental model/diet	Animal
Cholesterol 0.1%–25%	mouse, rat, guinea pig, rabbit, quail, cockerel, minipig, rhesus monkey, baboon
Wool fat (lanolin)	rabbit
Olive oil	minipig
Beef tallow Egg-yolk Triton	rabbit baboon rat, minipig
Others	
EPL (bio-availability pharmacokinetics)	rat, rabbit, dog, rhesus monkey
EPL (<i>in-vitro</i>)	endocytosis, LCAT activation, cholesterol uptake into EPL vesicles

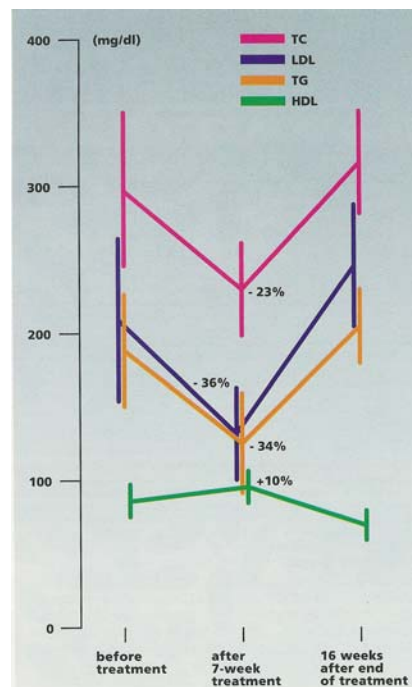
As can be seen from the table above, different diets have been applied in various species in order to promote disorders of lipid metabolism comparable to those found in man.

6.1 Reduction of Serum Lipids

Using one of the noxae mentioned in the table above, an increase in serum lipids was triggered over a minimum of 2 weeks to a maximum of 18 weeks.

Species	Diet	EPL administration
Mouse, rat, Rabbit, cockerel, Minipig, Rhesus monkey	high-cholesterol wool fat, tallow, Triton (acute, subacute), olive oil i.v., egg yolk	oral/ i.v./ i.p./ intracardiac preventive/ concurrent/ curative

In the experiments of E.K. Wong et al (72) rhesus monkeys were fed a high-cholesterol diet over a period of 10 years (fig. below).



Investigations on rhesus monkeys (n=7) after a 10-year period of high cholesterol diet (120 mg/100 kcal) and a 7-week period of polyenylphosphatidylcholine application (1.7 g/100 g diet). Assessment of serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride values at baseline, 7 weeks after the start of medication and 16 weeks after completion of the medication.

6.2 Effects on Lipoproteins

The action of EPL was reflected in an increase of HDL cholesterol and a decrease in LDL cholesterol, VLDL triglycerides as well as reduced ratio of LDL/HDL cholesterol.

T: Yasugi et al (73) observed a drop in the LDL cholesterol of isolated rabbit aortas after administering EPL. When macrophages from the peritoneum of rats were incubated in a medium to which EPL vesicles were added, these vesicles took up increasing amounts of radiolabelled cholesterol from the macrophages in a manner similar to that whereby cholesterol is taken up by HDL (61).

O. Zierenberg and his group (74,76) carried out comprehensive studies on the EPL pattern in lipoproteins after oral or intravenous administration to rats, rabbits and dogs. Depending on the individual species 50 to 80 % of the activity administered was traced to HDL and about 20 % to LDL and VLDL after intravenous administrations of radioactively labelled EPL.

Species	Diet	EPL administration	
Rat, rabbit, Dog, minipig, Rhesus monkey, Chimpanzee	high-cholesterol wool fat,	oral/ i.v./ i.p.	concurrent/ curative

Table 12: Selected refs: 54-58, 61, 72-74, 76, 78

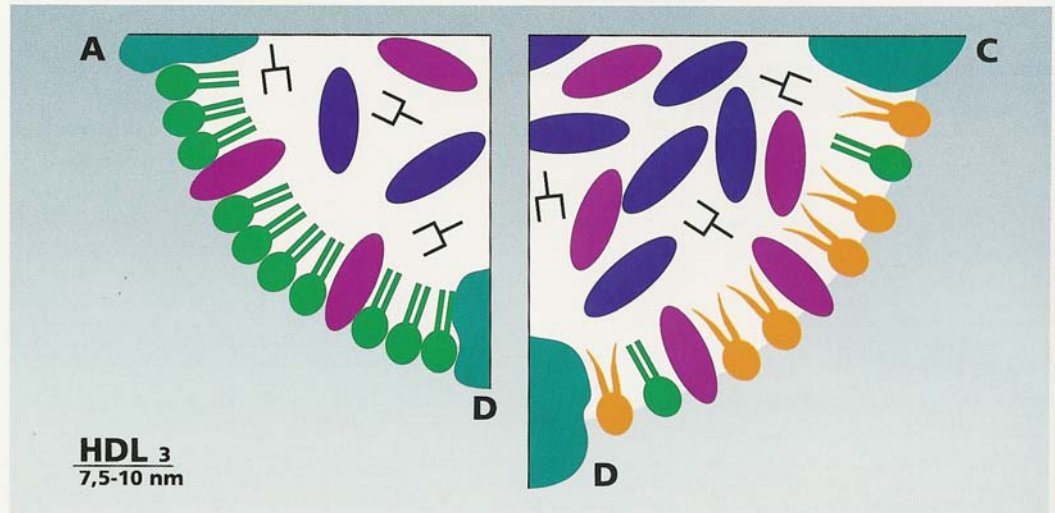


Fig. 13a: Normal surface capacity for cholesterol uptake

Fig. 13b: Increased surface capacity after EPL incorporation

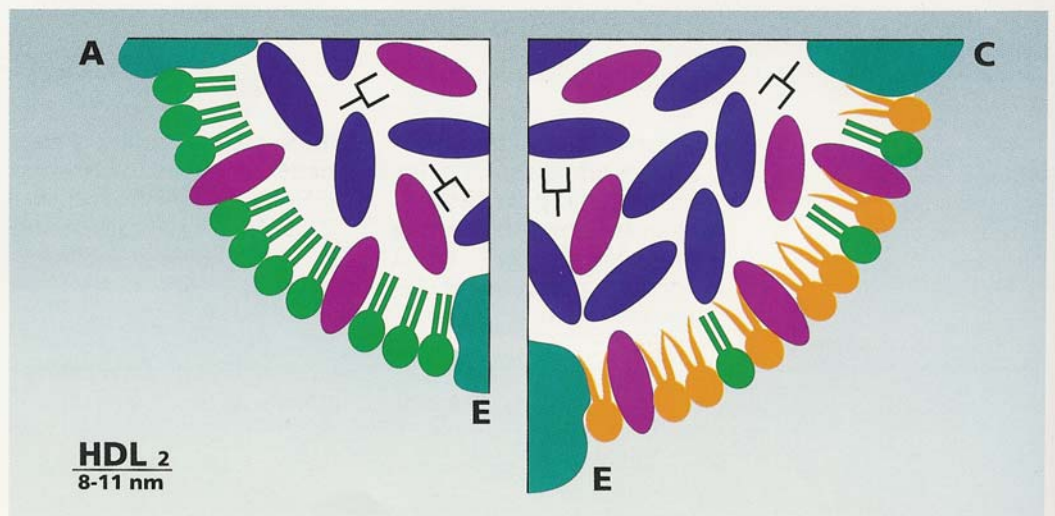


Fig. 14a: Normal cholesterol ester content

Fig. 14b: Enhanced cholesterol ester content after EPL incorporation



6.3 Influence on Enzyme Activity in Serum and Aorta

Species	EPL-administration	
Rat, Rabbit, Baboon, Chimpanzee	oral/ i.v./ in vitro incubation	preventive/ concurrent/ curative

Selected refs 18,20,24,25,27-29,46-49,51-53,60,69,78

The influence of essential phospholipids on the essential enzymes of fat metabolism was studied after intravenous applications as well as after in vitro incubation. C. Desreumaux et al. (20) obtained lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) from the adipose tissue, myocardium, lungs or the livers of rats and assessed enzyme activity after in vitro incubation with either dipalmitoylphosphatidylcholine, egg-lecithin or EPL (table below). The highest increase in activity was achieved under EPL.

These results are in accordance with those obtained by I. Zulic et al (78) after intraperitoneal administration of EPL to rats. Similarly V. Blaton et al (18) observed a rise in the activity of milk lipoprotein lipase under EPL.

Several authors report an increase in the activity of cholesterol-esterase (27-29,47,48,69) while the activity of acyl-CoA-cholesterol-acyltransferase (ACAT) (27-29,46,47,69) was found to decrease after a 2 to 6-month application of EPL. In addition some authors (25,49,51,60) observed that the activity of lecithin:cholesterolacyltransferase (LCAT) increases.

Phospholipid in the incubation medium	HTGL* in the liver	LPL* in the heart	LPL* in the lungs	Adipose tissue
EPL	100	100	100	100
Egg-lecithin	43	60	70	71
Dipalmitoyl-lecithin	1	10	8	7

Influence of the type of phospholipid on the lipolytic activity in different tissue of rats (n=9). The dependence of the degree of saturation is presented as an index of activity which is relative to EPL= 100 (according to [20] Phospholipid concentration/ml incubation medium: 0.35 micromol/l.

* HTGL= hepatic triglyceride lipase, LPL= lipoprotein lipase

H. Shigematsu et al (60) who performed these tests with rabbits after a single intravenous injection of radiolabelled EPL, observed an increase in cholesterol esterification with linoleic acid and a higher uptake of labelled cholesterol esters into serum lipoproteins due to the activation of LCAT.

These results are in agreement with those of H. Peeters et al (49) and M. Rosseneu et al (51).

A.K. Horsch et al (25) obtained confirmation in cultures of thoracic aorta explants for a preferred esterification of cholesterol with linoleic acid after a 2-month period of intravenous EPL administration (200 mg i.v. three times weekly) in rabbits.

L. Samochowiec et al (54-58) reported the same phenomenon.

6.4 Effects on Atherosclerotic Changes

Species	EPL-administration	
Rat, guinea pig, Rabbit, cockerel, Quail, minipig, Pig, baboon, Cell cultures (Human aortic tissue)	oral/ i.v./ i.p./ <i>in vitro</i>	preventive/ concurrent/ curative

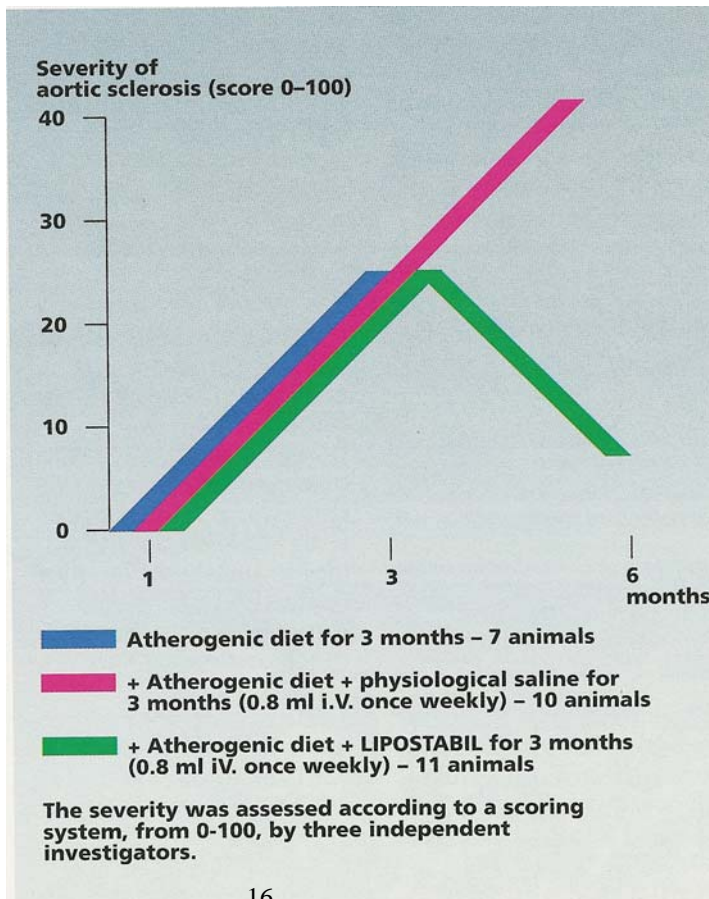
Selected ref: 19,21,22,27-29,31,32,41-44,46,52,53,55-59,61,63

The release of cholesterol (mg/g) from cells and tissue was measured following the incubation with EPL of subendothelial cells from the intima of atherosclerotic human aortas and tissue sections from the aortic intima. Cellular cholesterol content was lowered in comparison to that of untreated cell cultures by up to 40% (31).

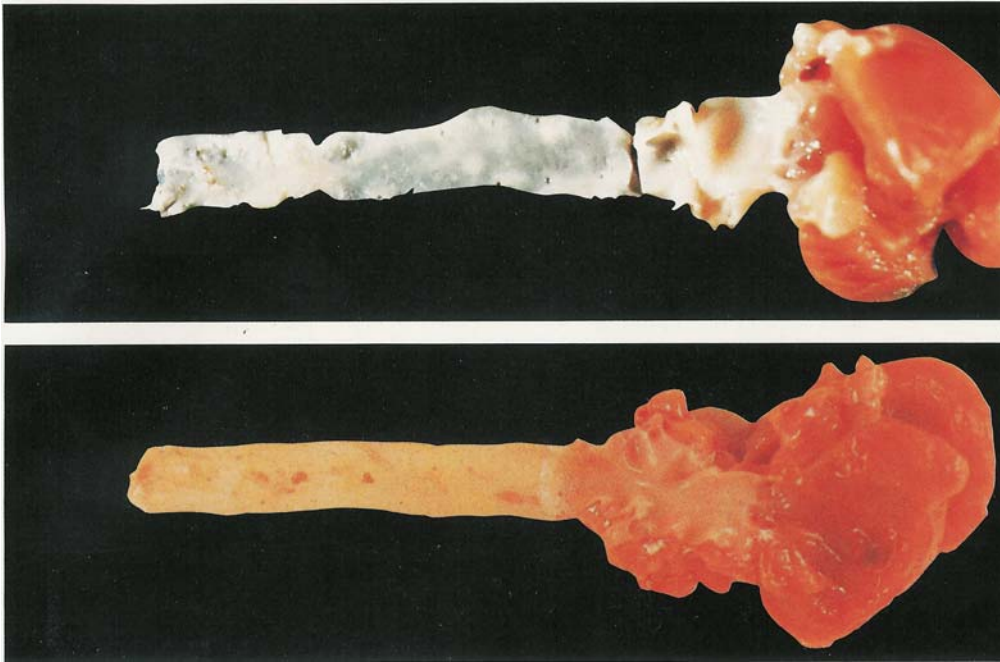
Atherosclerotic changes in vascular walls similar to those in human atherosclerosis were induced in the above species by a high-cholesterol regimen of at least 6 weeks and maximally 6 months. Several authors investigated the effect of EPL under concurrent application of the atherogenic diet.

B.C. O'Brien et al (44) did not find any fat deposits in the isolated aortas of EPL-treated guinea pigs. Neither did other studies (21,32) produce any evidence of a formation of aortic atheromas in rats after concurrent EPL treatment for a period of 3 months.

The coronary and aortic lesions observed in other experimental models (quail, cockerels, rats) (35,41-43,52,55,57,59,63) were clearly less pronounced in the animals treated with EPL than in the controls.



Where EPL was given only after discontinuation of the 6-month high-cholesterol dietary regimen, either a marked regression of the atherosclerotic changes in aortas and coronary arteries was observed (22,27-29) or the atheromas were found to disappear completely (35,51,52,54,55,57-59). The Fig. on the left shows the results of investigations carried out with quails by W.W. Stafford and Ch.H. Day (63). After feeding an atherogenic diet to all birds for 3 months, some of the animals were killed and the severity of vascular wall changes assessed (group 1). For another 3 months the other 2 groups then either received saline injections (group 2) or EPL injections (group 3) together with their atherogenic diet. Contrary to the two untreated groups, a regression of the atherosclerotic changes in the vascular wall was demonstrable in group 3 and the deposition of cholesterol esters in the vascular walls proved to be significantly lower than that in the controls.



Semilunar valves,- ascending and descending branches and aortic arch of a rat after 2 months of a high-cholesterol diet. Note the nodular changes on the aortic valves and in the intima (according to 57).

Semilunar valves, ascending and descending branches and the aortic arch of a rat after 2 months of a high-cholesterol diet and subsequent 2-month administration of EPL together with normal diet (according to 57).

Some authors have closely associated the reversal of experimental atherosclerosis with the EPL – induced activation of LCAT and cholesterol esterases which prevented or reversed an accumulation of cholesterol in vascular walls (27-29).

In another experiment (26) the aortas of rabbits were explanted after an 8-week high-cholesterol diet, to prepare tissue cultures. The release of cholesterol esters from the aorta explants was significantly higher in the cultures of tissue obtained from animals pretreated with EPL than in controls.

In addition, D.E. Bowyer et al (19) described a highly significant inhibition of endocytosis in the smooth muscle cells of pig aortas

after in vitro incubation with EPL. According to the authors these results suggest that EPL effected an inhibition of atherogenic processes by reducing the endocytosis of plasma constituents.

The figures above come from an experiment by L. Samochowiec et al (55,57), where rats were fed a high – cholesterol diet for 60 days. Some of the animals received concurrently daily EPL. Others only received the same doses of EPL after they had been taken off their 60 day diet. The third group served as controls and did not receive the test substance. While the control aorta explants showed fatty infiltrations, no atherosclerotic changes were demonstrable in the aortas of the two other groups or they were markedly less pronounced.

6.5 Influence on Prostaglandin Synthesis

In *in vitro* studies on seminal vesicular microsomes of rats the presence of EPL in the incubation liquid (100 micromol/l) stimulated the formation of 6-keto-PGF 20-fold above that in medium without EPL or that in egg yolk phospholipid-enriched medium.

In another study 3 h after rats had received 300 mg PPC/kg *i.p.* ring preparations of their aortas were incubated in a medium containing 1-C- arachidonic acid. The labelled prostaglandins were measured by means of a radioactivity monitor, as in the afore-mentioned trial. The formation of prostacyclin was found to have increased to double the control levels, while the administration of egg yolk phospholipids to rats under similar conditions did not produce a rise in prostacyclin synthesis.

It follows, therefore, that polyenylphosphatidylcholine intensified the enzymatic conversion of PGH₂ to PGI₂ (6-keto-PGF) at the expense of PGE₂. The effect was dose-related and significant (34).

6.6 Effects on Hemorrheology

In vitro results with EPL indicate a decrease in platelet sensitivity to substances promoting aggregation (31). Platelet suspensions obtained from human plasma were pretreated by adding EPL at different concentrations (250 – 2500 micrograms/ml) before inducing platelet aggregation with PAF/collagen or ADP. Complete inhibition of the ADP-induced aggregation was produced by 2500 micrograms of EPL/ml, while platelet aggregation induced by PAF/collagen was already prevented by 85.1% ($p < 0.01$) with a solution of 250 micrograms of EPL/ml.

6.7 Influence on Lipid Peroxidation

In vitro LDL (nLDL) obtained from the serum of volunteers showed an increase in lipid peroxidation under oxidative stress (O₂-LDL). Simultaneous incubation of the LDL with EPL significantly inhibited the increase in lipid peroxidation products (maloneadialdehyde, diene conjugates, oxidized triglycerides) in the medium as compared with O₂-LDL (17).

Excessive lipid peroxidation in rats in which liver damage had been induced by toxic doses of tetracycline, was suppressed by concurrent (62) or subsequent administration of EPL (50). This antioxidative effect was pronounced in comparison with control values.

Under similar test conditions E.A. Ortenberg and E.I. Zhikhareva (45) found a more marked lowering of maloneadialdehyde levels in rat liver homogenates after one month of EPL injections than in the controls.

Moreover, the results of H. Jaeschke et al (30) and A.I. Vengerovsky et al (68) confirm the antioxidative action of EPL. The studies of A.I. Vengerovsky et al. showed the formation of diene conjugates, Schiff bases and maloneadialdehyde as well as the drop in glutathione to be less pronounced than in the control animals not receiving EPL.

As W. Klinger reported at the Asian Pacific Association for the Study of the Liver in Djakarta in 1990; a 10-week application of 100 and 300 mg of EPL/kg b.w. to ageing rats not only resulted in a decrease in aortic lipid peroxidation products,

but also in an increase in glutathione levels in the liver, plasma and aortic tissue of rats in particular. The glutathione-dependent antioxidative capacity in the aortic walls was found to increase markedly. As a whole, the values of the investigated parameteres approached those of the young rats. Hence EPL produced, under the given test conditions, distinct antioxidative effects.

6.8 Experiments of the Simulated Transport Function of HDL

Research groups from Chicago, London, Moscow and Chiba/Japan (33,61,65-67,70,71) developed and investigated lipoprotein-like phosphatidylcholine particles in an attempt to simulate HDL function.

They either prepared phosphatidylcholine (PC) liposomes or used EPL solution containing EPL in the form of micelles.

These preparations were screened in vitro as well as in vivo, after intravenous injections into animals, for possible HDL-like cholesterol transporting properties. Provisional results from the different groups suggest the following:

A high linoleic acid content of the PC-particles, positively charged surface PC-layers and a low particle microviscosity are co-determining factors for HDL-like properties.

Among the phosphatidylcholines tested, EPL was the most active with regard to the uptake of cholesterol and the formation of complexes with it in an HDL-like manner (66,67). The complexes of EPL and apolipoprotein A-1 prepared by another group (33) displayed a similar density to that of HDL particles. They also proved identical in their plasma clearance pattern.

After the injections there was a slight transient increase in serum total cholesterol indicating the complex binding of cholesterol with the micellar PC; however, this was followed by a distinct drop of cholesterol level in serum (33,48,63,70,71).

Liver uptake of the cholesterol-loaded EPL particles did not seem to depend on identification by LDL-receptors (70): during a high-cholesterol regimen, even in rabbits lacking LDL-receptors, cholesterol was mobilized from the vascular walls, was bound to EPL particles and taken up by the liver.

Taken together, these results are promising as regards the tissue extraction of cholesterol into plasma. They suggest that EPL might be considered as a compensatory treatment for inadequate cellular cholesterol release, for instance in human receptor-deficiency atherosclerosis or ischaemic heart disease (67).

On summarizing the data compiled in animal experiments, it becomes obvious that under the given test conditions EPL prevents the development of hypercholesterolaemia/hypertriglyceridaemia and, at therapeutic doses, normalizes LDL cholesterol, total cholesterol as well as triglyceride levels in the serum. In addition, phospholipid controlled processes are promoted, so that an inhibition of the pathological tissue accumulation of cholesterol as well as a mobilisation of its reverse transport from vascular walls is achieved, for instance by the activation of lipolytic or cholesterol-esterifying enzyme systems (LPL, HTGL,LCAT), by inhibition of ACAT, by increasing the HDL capacity for cholesterol uptake and by stabilizing the cholesterol reverse transport system. Moreover, indications were obtained for a cytoprotective and antioxidative action as well as an improvement of platelet and erythrocyte fluidity.

7. Clinical Studies on EPL

7.1 Effects on Serum Cholesterol

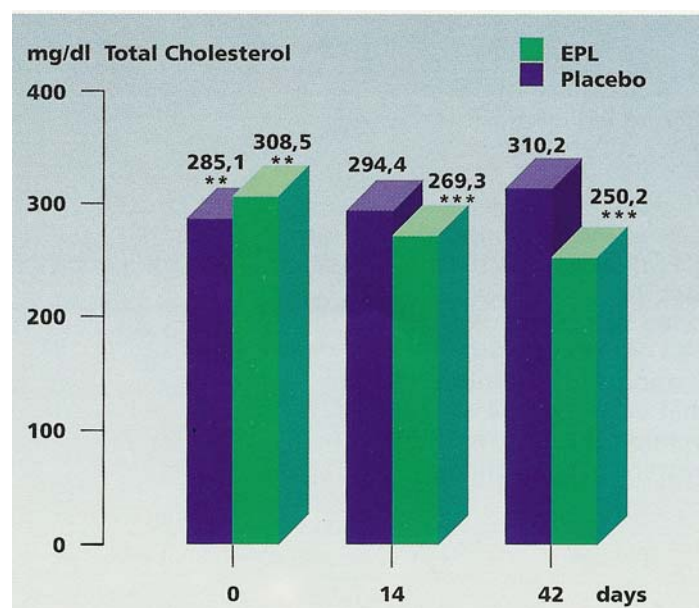
The response of total serum cholesterol to EPL treatment has been assessed clinically in 3836 patients. Especially in the early studies (up to 1969) this parameter served as the main basis for an evaluation of the influence of EPL; this was due to the fact that more sophisticated diagnostic methods had not yet gained ground, for one thing, and that authors were of the opinion that the reaction pattern of total cholesterol decided that of blood lipids, for another.

Reduction of Serum Cholesterol

In the majority of trials an average reduction of total serum cholesterol by 12 to 19 % was observed under treatment with EPL; in some of the trial groups mean values were reduced by more than 20 % as against initial values, yet others were lowered by 7 to 10 % only.

In a documentation of 15 clinical trials with a duration of EPL treatment ranging between 1 and 12 months, total serum cholesterol was lowered by 8.8 to 28.2% (107). The level of initial values, the route of administration, EPL dosage and duration of treatment seem to be the main determinants for the slope of the reduction. Nine to 20 days of intravenous EPL treatment for instance, already caused a reduction of total serum cholesterol of approx. 13 % (91,92,95,144,146).

An initially simultaneous administration of EPL ampoules and capsules led to a pronounced decrease in cholesterol (82); the author had introduced treatment on a dosage scheme of 250 mg i.v. + 875 mg orally and observed a further, though markedly slower decrease in cholesterol concentration when continuing treatment on oral EPL alone (chart below).



Lowering of serum total cholesterol in patients (n=13) with hypercholesterolaemia type II2 and IV after a 14-day double-blind treatment with 1,8 g EPL/day compared to controls (n=15). **=2p<0.01, ***=2p<0.001 (Wilcoxon matched pairs signed rank test)

After an initial 2-week intravenous administration of 1 g of EPL/day H. Peeters et al. (144) even registered a slight rise in serum cholesterol values when therapy was continued orally on 1,8 g EPL/d, though they did not return to initial values.

Under oral treatment (1,05 to 2,7 g of EPL/d) successful lowering of total cholesterol obviously depended on basal values at the onset of therapy: starting from moderately elevated total cholesterol levels (up to approx. 400 mg/dl) the reduction became all the more noticeable, the higher initial levels had been (116,119,124,144,147,158,161,175,177).

Duration of treatment

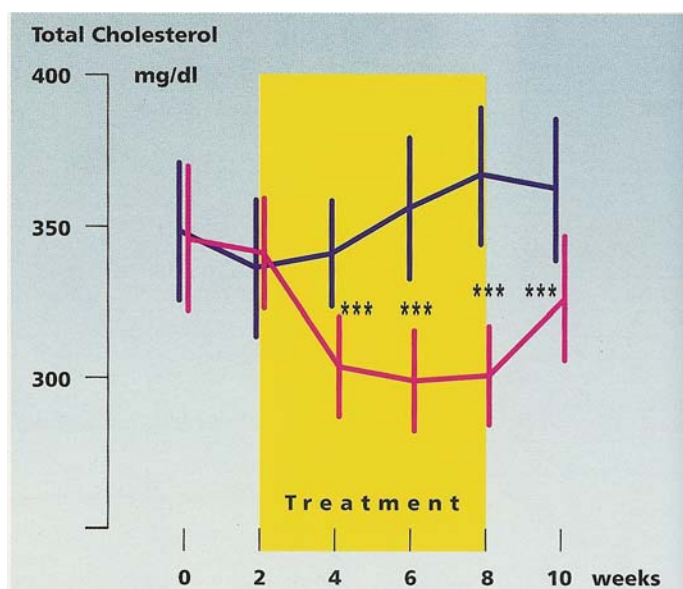
The duration of treatment is of varying importance for a reduction of total cholesterol. In trials using intravenous EPL. The preparation was only administered for a period of 9 to 20 days in most cases. In spite of these short periods of time the reduction of total cholesterol levels in serum proved satisfactory (mean values between 12,6 and 13,8 %).

Oral administration of EPL mostly covered periods of 4 weeks to 6 months. 12 trials involved long term studies which included at least a small number of patients who had been subjected to treatment periods of 9 to 24 months (81,118,121,132,136,150,143,147,161,162,173,180).

Some investigators (95,147) reported slight transient elevations of serum cholesterol at the beginning of treatment. According to the authors mobilization of cholesterol from vascular walls can be offered as an explanation for this phenomenon in atherosclerotic patients.

Moreover, it is assumed that with increasing age there is a slowing down of cholesterol clearance, which also may be responsible for the effects observed.

In contrast to these results a double-blind trial by A.K. Horsch et al. (117) using 1.8 g of oral EPL/d led to mean reductions of total cholesterol by 12,7 % already within 14 days of treatment. After another 4 weeks reduction of initial values totalled 18,9 % ($2p < 0.001$)- see chart below.



Total cholesterol in serum during a 6-week double-blind treatment with PPC (2.7 g/day orally) and a 2-week follow-up period without medication in patients (n=10; red line) undergoing dialysis for at least 1 year in comparison with controls (n=10; blue line).

After oral EPL treatment over 3 to 4 (to 16) weeks, mean rates of cholesterol reduction in another 4 studies (96, 163, 172, 178) that were either controlled against a diet, double-blind or were open, ranged from 12 to 25 % as compared with initial values.

Diet Plus EPL

While a diet alone did not produce satisfactory reductions in most cases, it clearly enhanced the effect on serum lipids when applied together with EPL (127, 172, 177), G. Varkony (177), for instance, observed that in spite of continuing the diet, serum cholesterol rose once more when EPL treatment was withdrawn and decreases only when therapy was taken up again.

Authors/Year	Oral EPL g/d	Treatment in weeks	Mean values in mg/dl		Decrease in %
			before	after	
H. Sekimoto et al. 1972	1.5	4	238.5	203.8	14.6 2p<0.05
T. Yasugi et al. 1973	1.5	4	256	222	14.0 2p<0.01
H. Nakamura et al. 1973	1.5 + 0.25 i.v.	4	248.6	224.3	9.7 2p<0.05
J. Schneider et al. 1979	1.8 + clofibrate	2x4	241	221	8.2 2p<0.01
M. Sznajderman 1985	1.8	8	330.0	305.0	7.5 2p<0.01
G. Nosedá et al. 1985	2.7	6	324.2	275.8	14.9 (IIa) 2p<0.05
P. Dewailly et al. 1985	2.7	6	321.7	277.4	13.8 2p<0.05
A.K. Horsch et al. 1986	1.8	6	308.5	250.2	18.9 2p<0.001
R. Kirsten et al. 1989	2.7	6	340.9	301	12.6 2p<0.001

7.2 Effects on LDL Cholesterol in Serum

Being the main carriers of cholesterol, low-density lipoproteins (LDL) are particularly atherogenic.

High levels of LDL cholesterol in serum damage the vascular endothelium and in this way facilitate a receptor-independent cholesterol diffusion through vascular walls. In other words, apart from the receptor-mediated physiological uptake, there is another, uncontrolled uptake of cholesterol leading to an enhanced accumulation of cholesterol in the cells.

Preventive therapeutic measures against the manifestations of atherosclerosis, therefore, aim predominantly at lowering serum levels of LDL cholesterol.

According to the present knowledge, LDL cholesterol levels permit a relatively reliable rating of the risk of coronary sclerosis to be made. This function of LDL is backed by sound and acknowledged pathophysiological mechanisms.

The response of LDL cholesterol to EPL treatment has been observed in clinical studies in approx. 1160 patients with the reduction of LDL cholesterol ranging from 10 % to 31 % of mean initial values. The extent of reduction was determined

by the type of hyperlipoproteinaemia involved, the homogeneity of the case material, the EPL dosages as well as the duration of treatment.

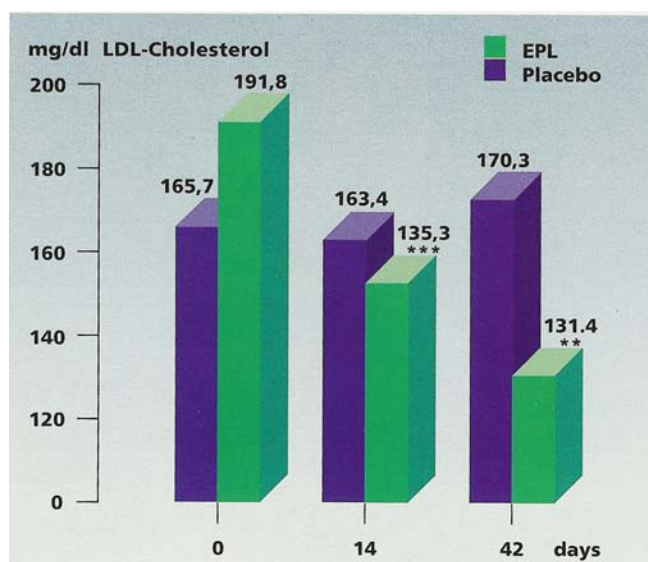
The study of H. Peeters et al (144) demonstrated the need for an adequately long duration of treatment. A 14-day treatment with 250mg/d of intravenous EPL did not lead to distinct changes in the serum profile of lipoproteins. According to U. Svanberg et al. (168), this initial failure to reduce LDL cholesterol may reflect an intensified catabolism of VLDL to LDL.

Reduction of LDL Cholesterol in Serum

P. Dewailly et al. (100) and A.K. Horsch et al. (117) carried out double-blind trials against placebo with oral doses of 2.7 g EPL/d or of 1.8 g EPL/d resp.; already on the 14th day of treatment they registered a drop in LDL cholesterol of 12 % and 20 % respectively.

In a controlled cross-over study (83) mean reductions of 25.8 % in the initial LDL cholesterol levels were obtained within a 2-month therapy period.

After a treatment period of up to 218 days M. Murakami et al. (138) achieved average reductions of 25.5 %; P. Saba et al. (151) observed a mean reduction of pathological initial values of 27.9 % within 129 days of treatment.



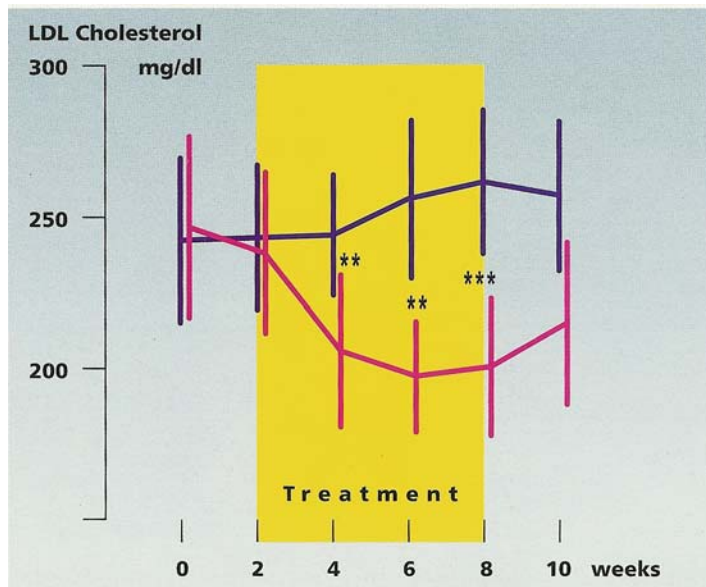
Lowering of serum LDL-cholesterol in patients (n=13) with hypercholesterolaemia type IIb and IV after a 14-day and a 42-day double-blind treatment with 1,8 g EPL/d in comparison with controls (n=15).
 =2p<0.01, *=2p<0.001

Reduction of LDL cholesterol in 7 double-blind studies. IIa= type IIa according to Fredrickson n.s. = not significant

Authors/Year	Oral EPL g/d	Treatment in weeks	Mean values in mg/dl		Decrease in %
			before	after	
H. Nakamura et al. 1973	1.5 + 0.25 i.v.	4	47.3%	45.8%	1.5 n.s.
J. Schneider et al. 1979	1.8 + clofibrate	2x4	123.4	122.8	rise in LDL prevented
P. Dewailly et al. 1985	2.7	6	222.4	186.2	16.3 3 weeks:12 2p<0.05
G. Nosedá et al. 1985	2.7	6	247.8	197.8	20.2 (IIa) 2p<0.05
M. Sznajderman 1985	1.8	8	250.7	225.7	10 2p<0.05
A.K. Horsch et al. 1986	1.8	6	191.8	131.4	31.4 2p<0.01 2weeks:20 2p<0.001
R. Kirsten et al. 1989	2.7	6	238.8	200.8	16 2p<0.001

Highest average reductions of LDL cholesterol, viz.: 41,3 % after 42 days of treatment, were recorded by A.K. Horsch et al. (117) in the double-blind trial described earlier.

In another double-blind trial (155) in which patients had received clofibrate and clofibrate plus EPL, J. Schneider et al. observed that EPL slowed down the rise in LDL cholesterol induced by clofibrate.



LDL-cholesterol in serum during a 6-week double-blind treatment with PPC8 2,7 g/day orally and a 2-week follow-up period without medication in patients (n=10; red line) undergoing dialysis for at least 1 year in comparison with controls (n=10; blue line)

**=2p<0.01,
***=2p<0.001

Cholesterol Esters

H. Ditschuneit (102) et al. obtained evidence for an increase in cholesterol linoleic acid esters in LDL, for instance, in a pilot study including healthy volunteers with diet-induced hyperliproteinaemia; this phenomenon had already been described by H. Peeters et al. in 1974 (144) and later was confirmed by V. Blaton (92). Blaton attributed the increase in LDL cholesterol esterified with linoleic acid to an activation of LCAT (see 7.6.1) and to an increase in the enzymatic activity of cholesterol esterase under EPL treatment.

This result is of importance because the rate of hydrolysis of cholesterol esterified with highly unsaturated fatty acids (e.g. linoleic acid) is higher than with saturated esters, so that while cholesterol linoleic acid ester is hydrolysed more rapidly, serum clearance of LDL cholesterol is accelerated too. This effect triggered by the administration of EPL is a step toward the prevention or inhibition of vessel wall lesions induced by atherogenic LDL cholesterol (92).

In summary it is safe to say that a distinct lowering of LDL cholesterol in serum has been achieved in almost all investigations with EPL. As the results of the LRCCPP Trial* have demonstrated, a decrease in cholesterol of 1% lowers the coronary risk to a patient by about 2%. Hence even a less pronounced reduction in total cholesterol and serum LDL cholesterol will be of decisive importance in the long run.

*Lipid Research Clinics Coronary Primary Prevention Trial (195)

7.3 Effects on HDL Cholesterol in Serum

In association with the LDL cholesterol levels HDL cholesterol concentrations (ratio) (as well as those of HDL subfractions and apoproteins) may serve as an indicator of the atherosclerosis risk of a patient, and in this capacity represent a criterion for the requirement for drug therapy of raised serum levles of cholesterol and triglycerides.

HDL suppress LDL-binding to smooth muscle cells and inhibit the proliferation of smooth muscle cells into the media of arterial vessels thus weakening the damaging effect of LDL cholesterol on the endothelium (190).

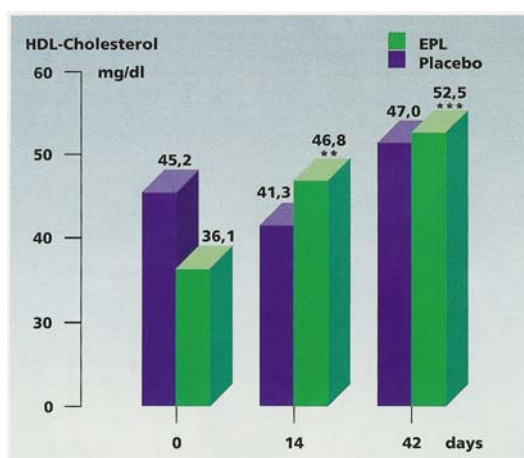
Consequently, any drug therapy is aimed at enlarging the HDL capacity for cholesterol uptake from LDL and the vascular wall, so that serum LDL cholesterol as well as total cholesterol are reduced and an accumulation of cholesterol in the vascular wall is prevented.

The following gives a survey of studies assessing the response of HDL cholesterol, of the HDL subfractions HDL2/HDL3, the apoprotein A-1 and/or the LDL/HDL cholesterol ratio to EPL treatment.

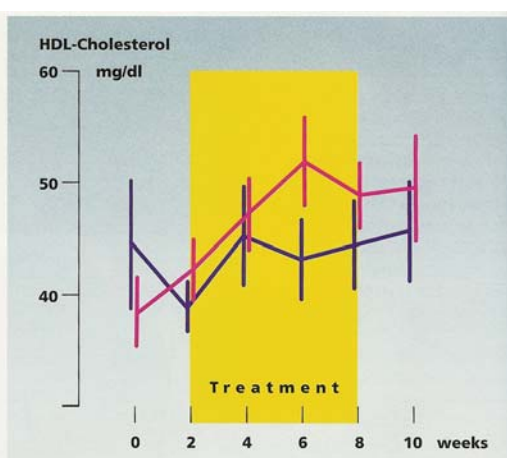
Increase of HDL Cholesterol in Serum

Various authors (88, 121, 140, 166, 173) have given values after lipoprotein electrophoresis as percent of the total lipoprotein content. Within 1 to 3 months of treatment with EPL, the HDL cholesterol of the patient groups investigated improved by 1.5 to 2- fold.

H. Izumi et al. (121) observed an increase in HDL cholesterol from 13.4 to 20 % of total lipoproteins (normal range) when subjecting diabetic patients to a 12-month oral treatment with 1.5 g of EPL daily. The authors of other studies (83, 89, 97, 103, 107, 117, 120, 124, 125, 134, 160, 167, 168, 171, 172) expressed mean HDL cholesterol in mg/dl or mmol/l. The increase rates obtained for HDL cholesterol as compared with initial levels ranged between 10 and 45 % with values above 20% being the most frequently described. It was obvious that low initial levels of HDL cholesterol were raised, while high initial values were hardly influenced or remained normal throughout treatment.



Increase of serum HDL-cholesterol in patients (n=13) with hypercholesterolaemia type IIb and IV after a 14-day and a 42-day double-blind treatment with 1,8g EPL/day in comparison with controls (n= 15).



HDL-cholesterol in serum during a 6-week double-blind treatment with PPC (2,7g/d p.o) and a 2-week follow-up period without medication in (n=10;red line) undergoing Dialysis for at least 1 year in comparison with controls (n=10;blue line).

In a controlled study V.K. Serkova (16) measured a mean increase in HDL concentrations from 1.1 to 1.42 mmol/l (+29 %) giving a significance of $p < 0.01$ ($n=42$).

A. Maeda et al. (134) conducted a controlled study ($n=32$) and reported mean elevations of 25 % ($2p < 0.001$). The increase in HDL cholesterol was most pronounced when initial values were lowest.

A. Fasoli (107) observed comparable reactions (mean increase in HDL cholesterol of about 26 %). He demonstrated a significant rise in HDL3 as well as HDL2 ($p < 0.01$).

Mean HDL cholesterol increases of 10 % were observed in the controlled study of T. Suo et al. (167). However, when patients were stratified (for low or high initial levels), the group with baseline values of 30 mg/dl ($n=17$) showed mean increases of 26 % ($p < 0.05$), while there was only a slight increase when initial values were higher than 50 mg/dl ($n=23$).

In his controlled study covering a 4-week treatment with 1.8 g EPL/d M. Tomasevic (172) observed a mean elevation of HDL cholesterol of 22 %, while a mean increase of 30 % ($n=5$) was reached in a patient group reported by U. Svanbert et al. (168). In their double-blind test against placebo, A.K. Horsch et al. (117) observed a mean rise in HDL cholesterol of 30 % after 2 weeks of treatment with 1.8 g EPL/d, while the corresponding value was 45 % after 6 weeks ($2p < 0.001$) – see table above.

In a double-blind trial by R. Kirsten et al. (125) dialysis patients ($n=10$) were subjected to EPL treatment: 4 weeks after the onset of therapy HDL had increased by 23 %, while at the end of the 6-week course of treatment the corresponding value was approx. 15 %.

EPL and Hemabsorption

In some studies EPL was given by intravenous and oral administration during and in between several hemabsorption sittings (89, 131). The authors reported a substantial reduction among others of total cholesterol and LDL cholesterol as well as a distinct increase in HDL cholesterol. The authors are of the opinion that the rise in HDL is to be attributed without doubt to the action of EPL.

LDL/HDL Cholesterol Ratio

This ratio was found to decrease from 4.3 to 2.8 in an open study including 14 patients who received a 4-week course of treatment with intravenous EPL injections of 0.5 to 1g/d (111).

The results of a controlled study by S. Uchida (174) showed that the decrease in the LDL/HDL ratio was clearly dose-related, i.e. it was most noticeable at doses of 1.5 to 2.25 g of EPL/d. In a controlled trial M. Tomasevic (172) observed a 24 % reduction of the LDL/HDL ratio ($n=30$).

A reduction of the LDL/HDL cholesterol ratio from 5.6 to 3.7 was observed under double-blind conditions of the trial by R. Kirsten et al. (125).

In comparative studies by E. Diamantopoulos and L. Varsou (101) a group of CHD patients showed a drop in the LDL/HDL cholesterol ratio to normal values ($p < 0.01$), while the ratio of patients suffering from hypercholesterolaemia but without CHD clearly approached normal values (< 2).

A substantial lowering of the LDL/HDL ratio indicating a lessened coronary risk has also been described in other controlled (165), controlled cross-over (83) or double-blind trials (141, 169).

A similar interpretation was placed on the increasing levels of HDL cholesterol observed when patients with acute myocardial infarction (84) were given a 2-month treatment with 1.8 g EPL/d. This rise was more strongly pronounced in non-smokers than in smokers and was significant as compared with controls.

A. Turnherr (173) claimed that in his studies an increase in HDL cholesterol coincided with improved elasticity of the vascular wall. He interpreted this as showing cholesterol mobilization from vascular walls and elimination of cholesterol by HDL.

Fatty Acid Profile in the HDL Cholesterol Esters

A number of authors (89, 92, 144, 153) have pointed out that with EPL the fatty acid profile in HDL among other molecules had improved: among the cholesterol esters transported in HDL, the proportion of cholesterol esterified with linoleic acid was found to be relatively higher under EPL treatment.

According to G. Salvioli (153) EPL stimulates the enzymatic activity of LCAT, which, in turn influences the rate of cholesterol transesterification (HDL as the preferred substrate for LCAT) – see 7.6.1.

7.8 Effects on Serum Triglycerides

According to the recommendations issued by the Consensus Conference of the National Health Institute, fasting triglyceride levels below 250 mg/dl do not necessarily indicate an increased cardiovascular risk if total cholesterol in serum is normal.

Fasting concentrations of neutral fat in serum exceeding 250 mg/dl do, however, constitute a determinant factor for the progression of atherosclerosis, especially when further risk indicators are present (100, 192).

This assumption is backed by the observation that the atherosclerosis risk is distinctly higher in patients suffering from endogenous hypertriglyceridaemia and in diabetics with high triglyceride levels.

As seen with the investigations on EPL, triglycerides in serum may vary considerably with the cold and warm seasons and high or low calorie intake connected with them (166, 183).

Hence any drug therapy which lowers raised levels of high-triglyceride lipoproteins should always be accompanied by a long-term reduction of carbohydrate supply in the daily diet.

The response of serum triglycerides and/or the triglycerides of individual lipoprotein fractions has been assessed in the clinical studies summarized below. Triglyceride data on a total of 2734 patients treated clinically with EPL have been compiled.

Reduction of Serum Triglycerides

The following reports give a wide range of reduction rates for neutral fats in serum, with values of around 25 % being the most common.

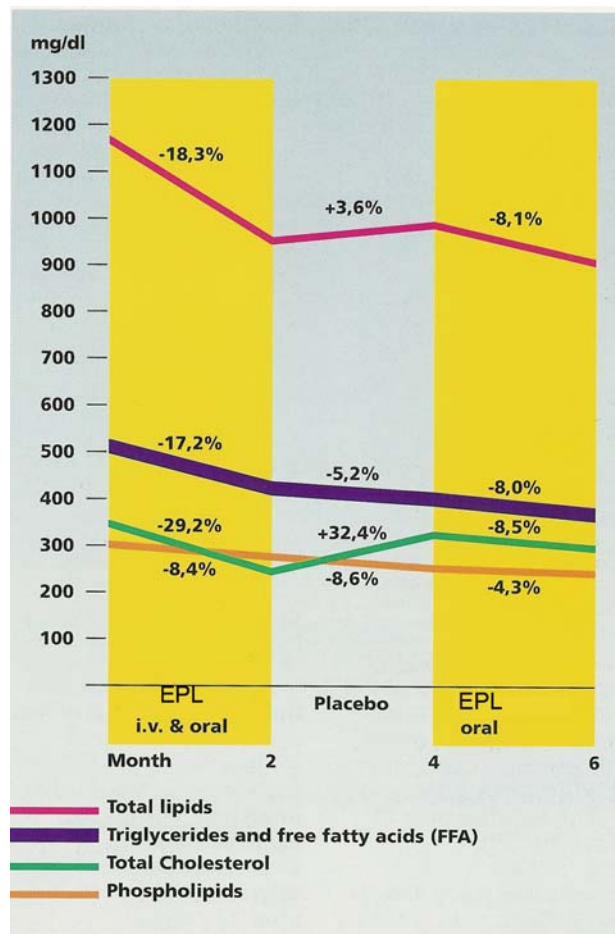
The extent of the reduction does not only depend on the duration of treatment and on EPL dosing. Several authors of controlled/double-blind trials have pointed out that relatively slight reductions of triglycerid levels in serum were achieved

when initial values had already been low or within the normal range (100, 178 179).

Moderately elevated initial levels of neutral fats in serum however fell from 195 mg /dl to mean levels of 146 mg/dl (approx. 25 %) (158), and from 198 to 134 mg/dl ($p < 0.001$) in diabetics (121) after 2 months oral treatment with 1.5 g EPL/d.

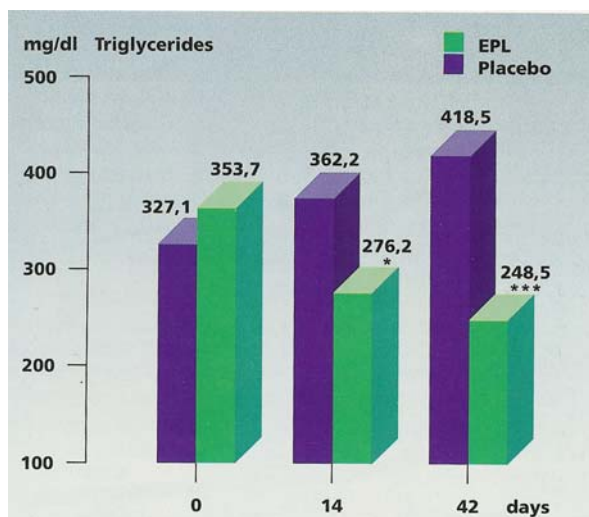
Several studies revealed a particularly rapid drop in serum triglycerides:

In a trial conducted by A.L. Grebenew et al. (112) 4 weeks treatment with EPL led to a marked reduction both in the patient group with high initial values (lowered from 274 mg/dl to 116 mg/dl) as well as in the group with only moderately increased baseline values (decrease from 201 to 94 mg/dl).



Percentage changes in the individual lipid fractions in the course of two-month treatment periods separated by a placebo period. (n= 17)

In a double-blind trial (117) with patients on a standardized diet mean values had dropped from 353,6 to 276,2 mg/dl (-21.9%) after only 14 days. (see chart on the right).



In a further study including patients with coronary heart disease and angina pectoris, investigators (79) reported a mean decrease in serum triglycerides of 23 % after 14 days of intravenous EPL injections of 1 g daily.

In a controlled study over three months T. Luther et al. (133) administered 1.4 g of oral EPL/d to patients after myocardial infarction. The mean decrease in serum triglycerides reached 24 % after 4 weeks and 46 % after 12 weeks.

Furthermore, the following research groups reported particularly marked reductions in serum triglycerides: table below

Authors	Reduction in TG in %	Treatment with EPL
KUKES et al. (130)	33.4	oral / 2 months
FAKHRI et al. (106)	34	oral / 2 months
UCHIDA (174)	34–37	oral / 2 months
UNGER et al. (176)	58	i.v. / 3 months
SABA et al. (151)	58	oral / 4 months

Influence of Nutrition or Occupation on EPL Efficacy

In a controlled study against placebo I. Zulic et al. (183) investigated the influence of the daily food intake on the lipid-lowering effect of EPL. No dietary recommendations were issued.

A 6-week treatment with EPL (1.05 g/d orally) produced mean triglyceride reductions of 22.7 % ($p < 0.01$) in winter when a greater supply of calories may be assumed, while levels dropped by 58.6 % ($p < 0.001$) under comparable conditions in early summer.

In another study (182) (controlled against placebo, 3 weeks oral administration of 1.8 g of EPL/d), when EPL was administered to subjects performing strenuous physical tasks with a correspondingly high calorie intake, serum triglycerides only decreased by 13.3 %, viz.: from 158.7 ± 50 mg/dl to 137.7 ± 48.2 mg/dl (significant as against controls). The levels of participants with office jobs, on the other hand (and correspondingly low calorie intake) could be reduced significantly from 171.9 ± 50 mg/dl to 97.3 ± 38.5 mg/dl (- 43.4%).

The use of EPL in Diabetes

Various investigators screened the possible influence of EPL on the disturbed fat metabolism of diabetic patients (81, 103, 121, 137, 146, 158, 161, 164, 176).

Treatment of the well-adjusted, insulin-dependent patients with maturity onset diabetes and diabetics on oral antidiabetic agents comprised a combination of EPL injections and capsules in the first 2 weeks, to be continued on capsules alone for the following 10 weeks.

Triglyceride levels in the insulin-dependent patients were shown to drop from 302 ± 58 mg/dl to 133.8 mg/dl on average; the respective values were 340 ± 67 mg/dl to 239.6 mg/dl for the controls (on oral diabetics). The authors explained this discrepancy in results on the basis of an insulin-related promotion of lipolysis (103).

The decrease in triglycerides was considered particularly favourable with regard to limiting the long-term complications of diabetes. In a trial against placebo (81), when 1.05 g of oral EPL/d had been administered to patients with maturity onset diabetes over a period of 12 months, triglyceride levels were 37.7 % lower than baseline values (from 210.6 mg/dl to 132.5 mg/dl). Under comparable test conditions (121) mean serum triglycerids of non-insulin dependent maturity onset diabetes were found to drop from 198 ± 24.6 mg/dl to 134± 15.8 mg/dl (p<0.001). No EPL-related influence on fasting glucose levels was observed.

Authors/Year	Oral EPL g/d	Treatment in weeks	Mean values in mg/dl		Decrease in %
			before	after	
H. Sekimoto et al. 1972	1.5	4	150.3	110.0	21.9
H. Nakamura et al. 1973	1.5 + 0.25 i.v.	4	221.0	194.9	4.9
T. Yasugi et al. 1973	1.5	4	148	132	10.8
I.D. Faulhaber et al. 1973	30	5 days	carbohydrate-induced increase in triglycerides prevented in healthy volunteers		
K.-J. Johannes et al. 1979	3	24	282.3	214.3 157.1	24; 12 weeks 44
J. Schneider et al. 1979	1.8 + clofibrate	2x4	391.0	333.0	15 2p<0.001.
P. Dewailly et al. 1985	2.7	6	190.0	194.0	n.s.
G. Nosedá et al. 1985	2.7	6	IIb: 265.7	223.8	15.7 2p<0.05
M. Sznajderman 1985	1.8	8	152.9	155.7	n.s.
A. K. Horsch et al. 1986	1.8	6	353.7	248.5	29.7 2p<0.001
R. Kirsten et al. 1989	2.7	6	327.2	283.9	13 2p<0.01

Effects on serum triglycerides in 11 double-blind studies.

As a whole, trial results showed a moderate to pronounced reduction of serum triglycerides to be attributable to EPL, with the patient's diet and the test conditions (duration of treatment, dosage, level of initial values) contributing further important determinants for the intensity of the reduction. Hence EPL influences both triglyceride levels and cholesterol levels in serum.

7.5 Influence on Lipid Peroxidation

Growing importance has recently been attributed to the part played by peroxides, particularly by lipid peroxides in cell membranes and lipoproteins, in the development and progression of atherogenic lesions in the vascular wall.

In the studies discussed below, the authors tested the possibility that EPL inhibits lipid peroxidation in coronary heart disease and diabetes mellitus.

The levels of acyl-hydro-peroxides, of Schiff bases, the diene/triene conjugates as well as malonedialdehyde and the intensity of haemolysis induced by peroxidation served as parameters when assessing the levels of the primary and secondary products of lipid peroxidation before and after EPL treatment.

In a controlled trial by V.K. Serkova (160) a group of patients with angina pectoris was subjected to 3-week oral therapy with 1.8 g EPL/d. At the end of treatment the reduction in atherogenic serum lipids and the rise in HDL cholesterol correlated well with the favourable effect on the indicators of lipid peroxidation and the signs of haemolysis due to peroxidation were reversed.

These results square with the observations of V.G. Spesivtseva et al. (164) had already reported in 1984 on a controlled study with EPL.

V.I. Kalmykova and E.B. Zakharova (123) were able to confirm these results in 1989 when carrying out a trial with patients suffering from stable angina pectoris (stages II-IV; n=104). Improved resistance of erythrocyte membranes was observed as a consequence of inhibited lipid peroxidation.

In a 12-week study S. Takahashi (170) demonstrated that the levels of baseline malonedialdehyde and their reduction rate were directly proportional.

V.S. Gurevich et al. (113) found a close interrelation between an increasing microviscosity of the platelet membrane - as a consequence of enhanced lipid peroxidation - and an increase in platelet activity, when investigating patients with unstable angina pectoris. The observation that lipid peroxidation was inhibited, therefore, was of particular importance because it suggested the possibility of a favourable effect on platelet activity which is intensified in this condition.

Together with a reduction of the atherogenic lipoprotein fractions in serum, the inhibition of lipid peroxidation following stimulation of protective factors by EPL provides a possibility for interrupting the progression of atherosclerotic changes in the vascular wall.

7.6 Effects on Enzyme Activity

7.6.1 LCAT

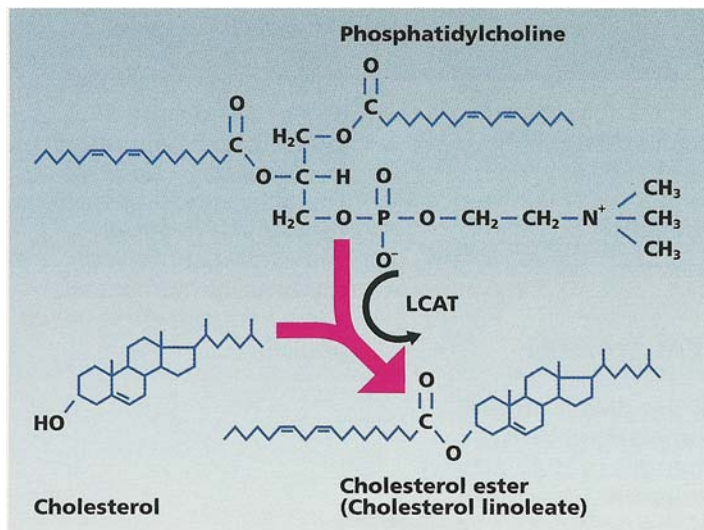
Lecithin:cholesterol-acyl-transferase (LCAT) – an enzyme that is synthesized in the liver and circulates in plasma- derives its overall significance from the catalysis of the esterification of free cholesterol in plasma. In this way free cholesterol on the surface of lipoproteins, erythrocyte membranes or in cells can be taken up by the HDL, be esterified and eventually eliminated from plasma (152-154). Increased esterification of free cholesterol leads to a marked enhancement of its transportation in the HDL core.

Qualitative and quantitative changes in the lipoprotein substrate (including a rise in the content of phospholipids with predominantly saturated fatty acids) cause diminishing LCAT activity in plasma. The supply of EPL rich in unsaturated fatty acids, on the other hand, activates the LCAT reaction (84, 89, 91, 92, 110, 134, 152-154, 160, 168, 170).

Hereditary LCAT deficiency may entail excessive cholesterol content in erythrocyte membranes of up to 90 % as compared with healthy controls and may interfere negatively with membrane rigidity and fluidity (Norum and Gjone quoted in: 154).

Catalysation of Cholesterol Esterification

LCAT catalyses the transfer of fatty acids in the 2-position of phosphatidylcholine to free cholesterol (see below). This reaction takes place in or on the HDL which are the preferred substrate of LCAT (91, 92). V. Blaton et al. (92) observed that the rate of cholesterol transesterification was promoted by enriching the HDL with EPL.



Phosphatidylcholine as the substrate for the formation of cholesterol-esters catalysed by the LCAT-enzyme.

The trial involved 93 patients with hyper-LDL-aemia or hyper-VLDL-aemia who received EPL injections (1 g of EPL/d) for the first 14 days; treatment was then continued for 69 subjects on an oral dosage scheme of 1.8 g of EPL/d.

The authors observed a close interrelation between LCAT activation and the EPL-related percentage increase in plasma cholesterol esterified with linoleic acid as well as the relative increase of these esters in HDL and LDL. The increase in cholesterol-linoleic acid esters was mainly localised in the HDL since HDL is the preferred substrate of LCAT. This indicated increased LCAT activity.

According to G. Assmann et al. (85) who investigated different phosphatidylcholines, including dilinoleoylphosphatidylcholine, the mechanisms of LCAT activation remain to be established.

Substrates	Relative activity (%)
C 18:2 linoleic acid	100
C 18:1 oleic acid	26.7
C 18:3 linolenic acid	1.1
C 18:0 stearic acid	0.4
C 16:0 palmitic acid	4.4

Presentation of the relative reaction rate of purified LCAT with phosphatidylcholine substrates which contain identical fatty acids in 1- and 2- position.

The highest transacylation rates were seen with 1,2- dilinoleoylphosphatidylcholine.

Radio-labelled phosphatidylcholine substrates 1 – pos. / 2 – pos.	Fatty acid composition of cholesterylesters derived form 1 – pos. (%) / 2 – pos. (%)	
palmitic acid / linoleic acid	3	97
stearic acid / linoleic acid	1	99
oleic acid / linoleic acid	8	92
linoleic acid / linoleic acid	40	60

After incubation of different phosphatidylcholine substrates and cholesterol with LCAT preparations the synthesized cholesterylesters were analyzed for the origin of the bound fatty acids.

In their opinion the formation of an LCAT/substrate complex and hence cholesterol esterification are facilitated by an increased fluidity of the PC substrate due to unsaturated fatty acid chains in the 1- and 2- position of the molecule as present in 1,2-dilinoleoylphosphatidylcholine.

U. Svanberg et al. (168) also considered the proper functioning of the LCAT reaction to be an elementary precondition for the catabolism of triglyceride transporting lipoproteins.

LCAT Activation

In the clinical studies summarized below, changes in LCAT activity represented just one of the parameters applied to measure the therapeutic success of EPL. A significant increase in LCAT activity ($p < 0.01$) was demonstrable under controlled test conditions (134).

A.S. Blagosklonov et al. (89), who used EPL in 83 cases in connection with hemabsorption to correct disturbances in lipid metabolism, considered the observed increase in HDL cholesterol to be related to EPL-induced intensification of LCAT activity and an enhanced mobilisation of cholesterol from vascular walls. V.K. Serkova (160) supported this view.

In the cases investigated, the tendency towards an increase in LCAT activity was most pronounced when baseline values were lowest (170).

In controlled studies G. Salvioli and his group (152-154) pursued the study of LCAT behaviour in liver disease and its possible activation by EPL. After 5 days

of EPL infusions of 2 g/d, LCAT activity increased from 31.2 micromol/l/h to 54.4 micromol/l/h on average.

The activation was reflected in a reduced cholesterol content of erythrocyte membranes and a reduced cholesterol/phospholipid ratio.

The authors considered the EPL-induced elevation of the linoleic acid content in the HDL as favourable for an improved fluidity of the particles, thereby facilitating the deposition of apoprotein A-1 and hence supporting the promoter function of this apoprotein for the formation of the LCAT/substrate complex.

These results derive substantial confirmation from another trial (110) involving patients with chronic liver disease. After 2 weeks of oral EPL treatment (1.8 g/d) the increase in LCAT activity correlated with an improved liver function in these patients.

7.6.2 Lipases

Lipoprotein lipases (LPL) as well as hepatic triglyceride lipases (HTGL) lyse the triglycerides in chylomicrons and very low density lipoproteins (VLDL). They thus initiate the transition of the VLDL into lipoproteins of higher density, that are crucial for the uptake and transport of cholesterol. Their enzymatic activity is governed by apoproteins and phospholipids (99) the unsaturated fatty acid content of which is of decisive importance in this context as has already been pointed out by V. Blaton and his team (90) in 1974.

	Adipose tissue	LPL+HTGL	Plasma LPL	HTGL
EPL	100*	100	64	36
Ovo-lecithin	46*	57	54	3
Dipalmitoyl-lecithin	16*	5	4	1

Influence of the type of phospholipid on the lipolytic activity in adipose tissues and post-heparin plasma of 9 healthy subjects. The dependence of the degree of fatty acid saturation is presented as an index of activity relative to EPL=100. Phospholipid concentration: 0.35 micromol/ml medium

C. Desreumaux et al. (99) isolated lipases from the tissue of healthy volunteers and incubated them in vitro with substrates of different phospholipids. Activation was highest when the LPL and HTGL had been incubated in an EPL-containing substrate, while the stimulation produced by phospholipids containing saturated fatty acids alone, was much weaker.

According to V.K. Serkova (160) the lipolytic action is further enhanced by the promotion of the dispersion of lipid macro-aggregates under EPL treatment.

In several trials I. Zulic et al. (181-183) have investigated LPL activation by EPL in comparison to placebo.

During a 6-week treatment period 80 patients with hyperlipoproteinaemia received 1.05 g of oral EPL/d; another study included 45 patients who were given 1.8 g/d of oral EPL for a period of 3 weeks. In the treatment groups the activity of LPL increased by 25 % and 40 % respectively, while no change was observed in the control groups.

V.G. Kukes et al. (130), who had administered 1.8 g/d EPL to 55 patients over a period of 30 to 50 days, also reported a significant increase ($p < 0.001$) in the activity of heparin-dependent lipolytic enzymes. The stimulation of lipoprotein lipase was most noticeable when initial values were low.

The results obtained in the controlled studies including 180 patients with hyperlipoproteinaemia, provide essential evidence for a lipase-stimulating effect of EPL which is to be seen in the context of the EPL- related reduction of serum triglycerides described in chapter 7.4.

7.7 Influence on Platelets and Red Blood Cells

7.7.1 Investigation into the influence of EPL on Increased Platelet Aggregation

S. Yoritsune et al. (179), among others, have described a close relationship between high lipid levels in serum and an increased tendency to adhesion and aggregation of platelets. Platelet aggregates are considered to be one of the factors contributing to atheroma formation in the vascular wall.

Deposits enhance the sensitivity of the vascular wall towards substances that are released from the platelets after their aggregation and which lead to an increase in vessel wall permeability. This, in turn encourages and accelerates the accumulation of further plasma constituents- such as lipids- in the injured wall. A leading role in stimulating the proliferation and migration of smooth muscle cells from the media to the intima is attributed to a growth factor that is synthesized and released by the platelets (platelet derived growth factor= PDGF).

Apart from a reduction of serum lipids under EPL treatment, the authors of the trials summarized below also observed a favourable effect on platelet membranes. Such investigations mostly involved patients suffering from coronary heart disease or diabetes, since the question of a possible effect on increased platelet aggregation is of particular interest in these diseases.

Over a period of 14 days V.A. Almazov et al. (79) administered infusions of 500 mg of EPL/d to 24 patients with angina pectoris. During this relatively short observation period they achieved a reduction in reactive platelet aggregation by approx. 60 % in comparison to baseline values ($p < 0.02$). Both the rate of primary and secondary aggregation and the interval until the aggregation peaks were reached were clearly diminished. Microscopic examination revealed a reduced number of aggregates and within them a reduced number of platelet conglomerates.

The authors explained this change in platelet activity by a qualitative and quantitative improvement of serum lipids due to the supply of EPL, by reduction of the cholesterol content in the platelet membrane, and by the exchange of membrane phospholipids with EPL. A significant inhibition of platelet adhesion to glass as well as an inhibition of platelet aggregation also has been described by S. Coccheri et al. (98) who administered 500 mg/d of intravenous EPL to 25 patients either as a single administration or for a period of 15 days.

S.S. Belousova et al. (88) also attributed the decrease in platelet aggregation observed under EPL to the shifting of cholesterol from the platelet membrane into the EPL-enriched HDL. Platelet aggregation was shown to slow down, which tallied with the results of V.G. Almazov et al. The optical density of the aggregates decreased. The changes did not vary during the 3-month follow-up phase after EPL treatment. Reduced platelet sensitivity towards substances provoking aggregation (e.g. collagen) became evident.

A similar phenomenon was described by O. Fakhri et al. (106). They used the relative dispersion of light transmission fluctuations as a parameter and measured platelet aggregation by means of an electronoptical analyser. 10 days treatment with 1 g i.v. EPL/d and 30 days of daily oral administration of 1.8 g EPL clearly reduced the sensitivity of thrombocytes to ADP (also ref. to 93). This was related to an inhibitory effect on the ADP-induced rise in Ca⁺⁺ in the platelets. Moreover, the authors observed an inhibition of PAF-induced platelet aggregation both in vitro and in vivo.

	PAT ± S.E.M.
before	2.79 ± 0.45
after 4 weeks	3.32 ± 0.78
after 8 weeks	1.68 ± 0.40
end (mean 15 weeks)	1.75 ± 0.49

PAT= platelet aggregation time in min after 10-12 min of rotation in a glass tube.
Platelet aggregation in hyperlipemic patients (type IIa, IIb, IV) before and after oral therapy with 3 g/day of EPL. Changes are significant for p < 0.05

In accordance with V.G. Almazov et al. C. Galli et al. (109) described a definite improvement in the composition of thrombocyte membranes:

6 weeks after the onset of treatment 7 healthy volunteers receiving 10 g EPL/d showed a reduction in total lipid content and cholesterol content, which was significant as compared with baseline values, while the phospholipid/total lipid ratio increased and a higher rate of esterification with linoleic acid in platelet phospholipids was observed. The authors regarded this as an indication of an exchange of phospholipids between cell membranes and the plasma compartment.

According to the authors, the incorporation of EPL into biological membranes like those of platelets, red blood cells and arterial walls might lead to an improvement of membrane fluidity and cellular function.

In association with reduced platelet aggregation V.G. Kukes et al. (130) observed an improvement of rheographical findings in their patients with chronic heart disease (see also 87,93).

R. Merchan and his group (135) arrived at similar results when administering i.v. injections of 250 mg/d of EPL over a period of 30 days in cerebral insufficiency of

the elderly. Fifteen and 22 days after the beginning of treatment the intensified spontaneous blood coagulation was found to decrease distinctly, while the thrombo-elastogram showed fibrinolytic activity to increase. Hence the platelet-related disturbance of the coagulation balance was being checked. These findings were confirmed later by S.S. Belousova et al. (88).

Some authors have associated the reduction in spontaneous platelet aggregation under EPL with a favourable influence on endogenous prostaglandin synthesis (94,142).

The study of T. Numano et al. (142) involved 11 patients receiving 1.5 g of oral EPL over 16 weeks. The authors observed an elevation in serum 6-keto-PGF₁α*) which was particularly noticeable in the 8th week, and a drop in thromboxane level (TXB₂). The significant reduction ($p < 0.05$) of the TXB₂-/6-keto-PGF ratio was interpreted as a cytoprotective effect of EPL.

*) stable metabolite of the antiaggregatory and vasodilatory prostaglandin PGI₂

The available reports clearly show that EPL reduces the enhanced tendency towards platelet aggregation resulting from disturbed lipid metabolism.

7.7.2 Investigation into the Influence of EPL on Red Blood Cell Fluidity

Structural changes in the red blood cell membrane resulting from an increased accumulation of cholesterol, i.e. a pathological cholesterol/phospholipid ratio, impair the fluidity and functioning of the membrane and limit red blood cell (RBC) deformability.

These changes obstruct the passage through the narrow lumen of capillaries and promote RBC aggregation thus adversely affecting the viscosity and flow properties of blood.

The resulting disturbances in microcirculation may contribute to a progression of pathological processes, especially where coronary heart disease, angina pectoris, retinopathy, and impaired cerebral or peripheral circulation are concerned.

A.M. Ehrly and his team (105) obtained evidence for an improved filtration of RBC through an 8 micron capillary filter after a single injection of 750 mg of EPL given to healthy volunteers; they suggested that this was due to improved RBC deformability. Fifteen and 45 min after the injection, both the filtration rate as well as the number of red blood cells per mm³ of the filtrate were higher than initial values, the same applies to the total number of the red blood cells filtered. Hematocrit as well as blood and plasma viscosity remained unchanged in these tests.

When patients with chronic occlusive arterial disease were examined under similar test conditions, the highest number of filtered red blood cells was detected 60 min after an i.v. injection of 750 mg of EPL ($p < 0.05$); 30 min later counts

almost equalled the initial values. The exchange of membrane phospholipids containing saturated fatty acids with EPL was considered a possible cause for the facilitated filtration of RBC and their improved deformability.

in man

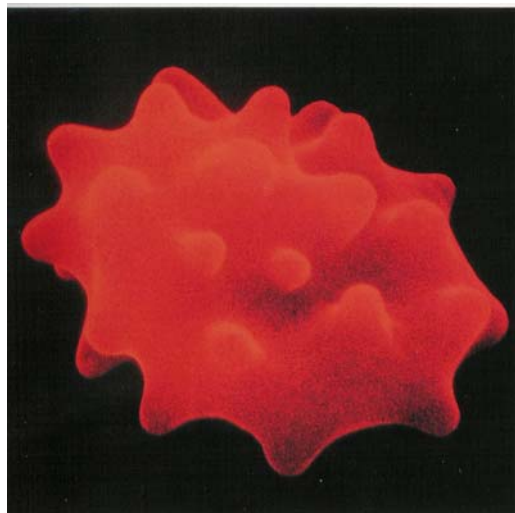
A.S. Blagosklonov et al. (89) confirmed an improved passage of red blood cells through microfilters (Nucleopore, USA) and the normalisation of RBC aggregation in their patient group. Parallel to haemabsorption their patients had received i.v. injections of 500 mg of EPL and after that had taken 1.8 g of EPL/d for 3 months.

The cholesterol/phospholipid index of RBC membranes dropped by 28 % to normal values. Contrary to A.M. Ehrly et al. (105) the authors did observe a normalisation in hematocrit and blood viscosity and an associated statistically significant rise in capillary flow.

The favourable influence on rheological findings and on lipid parameters correlated with an improvement of the clinical picture: depending on the severity of the coronary condition involved, these favourable changes persisted for up to 12 months after withdrawing from EPL.

In controlled studies involving patients with coronary heart disease (164) who received doses of EPL between 0.6 and 1.2 g/d, the rates of platelet and RBC aggregation did not reach those detectable in healthy volunteers. They were however markedly lower than those of untreated controls one month after the start of treatment.

Atherosclerotic patients also were subjected to a 4-week EPL therapy (1.5 g/d orally) under controlled conditions (179). In addition to other parameters, again the index of red blood cell deformability was improved and blood viscosity reduced. These findings are substantiated by the trial results of R. Merchan et al. (135) who administered 250 mg /d of EPL for 4 weeks.



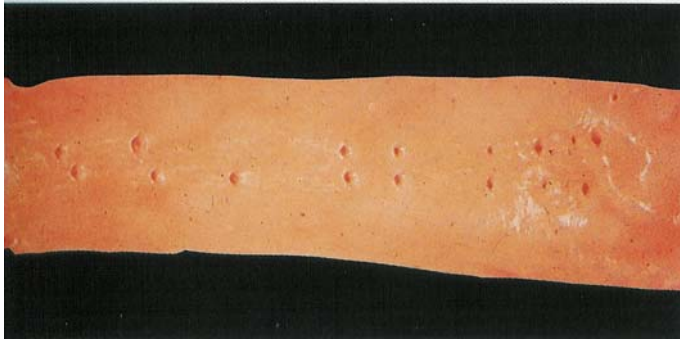
Irregularly contoured RBC surface due to increased Cholesterol/phospholipid ratio in the membrane

G. Savioli et al. (152-154) carried out extensive controlled investigations on the type and incidence of morphological RBC changes in liver disease.

According to their report the cholesterol increase in RBC membranes following a reduction in LCAT activity, provokes expansion and rigidity of the membranes with changes in RBC morphology in the form of uneven contours.

The authors infused 2 g of EPL/d over 5 days. As a consequence of the EPL related LCAT activation the cholesterol content in RBC membranes was

lowered and the cholesterol/phospholipid ratio decreased; at the same time membrane phospholipids were exchanged for EPL which increased the content of linoleic acids in the membranes. The changes in red blood cell morphology receded together with the reduction of the cholesterol/phospholipid ratio.



Aorta of a 44-year old woman. Status age-appropriate; remarkably tender intima virtually without lipoid infiltration or fibrosis.



Aorta descendens of a 78-year old man with wide spread liposclerosis, hyalinosis, calcinosis and ulcerated atheroma.

The study reports discussed substantiate the improvement in the fluidity of red blood cell membranes under EPL treatment. This is the result of a normalized membrane cholesterol content and/or the result of a relative increase in membrane phospholipids that are rich in linoleic acid (EPL). In combination with other parameters on which EPL exerts a positive influence, improvement in the fluidity of red blood cell membranes represents an essential contribution to inhibition of the progression of atherosclerotic changes in the vascular wall.

7.8 Influence on the Progression and Symptoms of Atherosclerosis

After evidence had been obtained showing that EPL lowers raised serum lipids, which constitute the no.1 risk factor for atherosclerosis in man (together with homocystein), it was clear that evidence for changes in the formation of atherosclerotic plaques in the vessel wall was required.

The results of animal experiments or studies on isolated tissue samples are promising, but are not fully applicable to man.

There are still no reliable models applicable to reversal of atherosclerosis in man. For a few years now it has been technically possible to observe atherosclerotic plaques on a long-term basis, to measure them and register their growth behaviour. Hence evaluation of a possible therapy-induced retrogression of atherosclerosis in man is no longer based on the subsidence of atherosclerotic symptoms alone.

In the studies available, EPL was used in atherosclerosis patients in order to study the effects described under 7.1 to 7.7 in combination with further measures, when the severity of the disease required this.

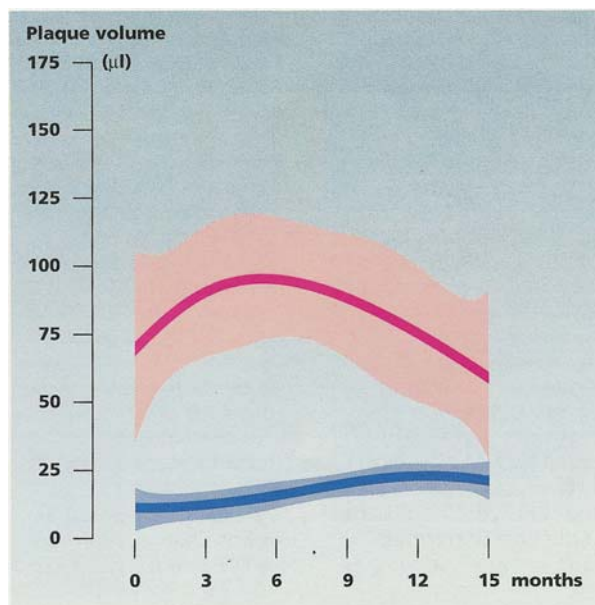
In the majority of studies attention was focused on the serum lipid pattern under EPL treatment with a reduction or normalisation of values serving as indication of a possible lessening of the atherosclerotic risk for the patient in question.

Results suggest that this may very well be feasible with prolonged administration of EPL. Moreover, additional evidence for a possible inhibitory effect on the progression of atherosclerosis has been established via a favourable influence on the flow properties of blood. In addition, the influence of an EPL-related improvement in serum lipid levels and the flow properties of blood on the given atherosclerotic symptoms was assessed, provided that sufficient numbers of large patient groups were available displaying a relatively homogenous localisation of the atherosclerotic lesion.

7.8.1 Measurement of the Size of Atheromas in Human Vessels

For 18 months a pilot study completed in 1989 kept track of the size of plaques by means of a real-time scanner covering sections of the superficial femoral artery as well as the carotid, iliac and popliteal artery (150).

Fifteen patients with asymptomatic atherosclerosis (stage I) were participating in whom at least one atheroma had been diagnosed at one of the sites mentioned. The participants took 2.7 g/d or oral PPC for at least one year. At the end of the observation period of more than 12 months the majority of the initial plaque volumes $\leq 25 \mu\text{l}$ tended to stagnate after a transient initial rise. Larger initial volumes ($>25 \mu\text{l}$) stagnated in most cases or showed a downward trend at the end of the 12-month observation period.



Total plaque volume during 15-month treatment with 2,7 g /day of EPL in 15 patients with a total of 57 plaques (150). 8 patients with an initial plaque volume > 25 µl: red line. 7 patients with an initial plaque volume < 25µl: blue line

7.8.2 Effects on Impaired Coronary Circulation

On the basis of objective findings and subjective symptoms patients with coronary heart disease (various stages of angina pectoris) or postmyocardial infarction conditions were assessed for a possible improvement of their condition.

Encouraging results from investigations on rats (187) have shown a protection by phosphatidylcholine of reperfused ischaemic hearts. Untreated isolated hearts subjected to low-flow ischaemia recovered 15 % contractility only (as compared to time-control hearts) following reperfusion, whereas contractility significantly enhanced to about 61 % (as compared to control hearts), if phosphatidylcholine was added 10 or 20 minutes before ischemia occurred. In addition, the incidence of arrhythmias during ischaemia and the following reperfusion were reduced.

ECG:

A number of studies have included ECG diagnostics (79, 80, 86, 118, 119, 130, 135, 136, 143, 148, 158, 160).

Depending on the severity of the disease, the EPL dosage and the duration of therapy, an improvement of ECG findings could be achieved in many cases.

Among others this was reflected in a dose-related reversal of pathologically changed terminal segments. S-T depressions were found to disappear; previously negative T-waves were reversed to positive.

These favourable changes indicated a relief of stenocardiac complaints.

Exercise tolerance as tested on the bicycle ergometer improved. The phase until S-T depression occurred became longer, with the depressions themselves being less distinct (79, 80, 130).

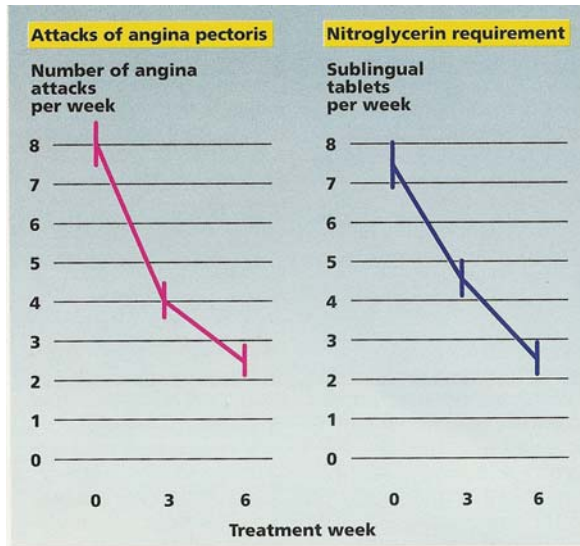
Incidence of Anginal Attacks, Nitro-Consumption:

All authors reported a decrease in anginal attacks (79, 80, 115, 118, 119, 130, 139, 158, 160, 164).

The investigations of V.A. Almazov et al. (79) included 34 male patients suffering from ischaemic heart disease and angina pectoris (stages III-IV); they received 500 mg/d of intravenous EPL for a period of 14 days. 20 of the 34 patients reported an absence of anginal attacks already at the end of the first/beginning of the second week of treatment. The other 14 patients experienced a reduction of attacks from 8 to 10 within 24 h to 1 to 3 attacks within 24 h, with the severity decreasing as well. Daily nitro-consumption therefore, could be reduced to 2 to 5 doses as well.

V.K. Serkova (160) who treated 42 patients with stable angina on exertion (stages II to IV) for 30 days on an oral daily dosage of 1.8 g of EPL, observed a 50 % reduction in the nitro-consumption of her patients.

Corresponding results have already been described by G. Hevelke et al. (115) in a multicentre study comprising 507 patients. (see figure next page)



Mean incidence of anginal attacks per week and consumption of nitroglycerin per week for patients with diminished coronary blood flow rates before and during a 6-week treatment with EPL.(n=507)

Subjective Symptoms:

For patients, the EPL-related subsidence of subjective complaints was of particular significance. In many cases patients experienced an increase in their exercise tolerance without pain after prolonged treatment.

In the trial group of V.A. Almazov et al. (79) the walking distance without stopping or requiring nitroglycerin was extended from 30-50 m to 3000 m.

In a controlled trial by L.D. Itkina et al. (119) geriatric patients with atherosclerosis suffered from fatigue, decrease in vitality, disturbed sleep, sensation of constriction in the heart region, retrosternal pain, palpitation. On completion of the EPL treatment 88 of the 94 patients reported a decrease in complaints and an increase in vitality. These changes were more pronounced after 2 months of treatment than after 1 month. Six of the patients did not experience any improvement due to the severity of the disease.

An increase in the physical and mental activity of the patients after EPL treatment was also observed by S.M. Idu et al. (118).

7.8.3 Effects on Impaired Peripheral Circulation

As with impaired coronary flow the stage of the disease will determine whether an improved permeability of vessels can be achieved.

In a controlled study comprising healthy volunteers and patients in stages I+II as well as III+IV of the disease (according to Fontaine) J. Klemm (126) demonstrated an improvement of blood flow in the muscles of the lower extremities after 30-day treatment with 1,8 g/d of oral EPL. This increase concerned both reactive hyperaemia as well as blood supply at rest. Flow velocity was raised as well, though slightly less in patients in stages III+IV due to longer collateral pathways.

The author assessed these changes in the light of a reduced blood viscosity, i.e. in association with an EPL-induced amelioration of flow properties rather than with a directly vaso-active influence.

Z. Luczac et al. (132) employed the oscillometric index as a measure of therapeutic success in occlusive vascular changes, using it to determine the patency of major vessels in 200 elderly male patients.

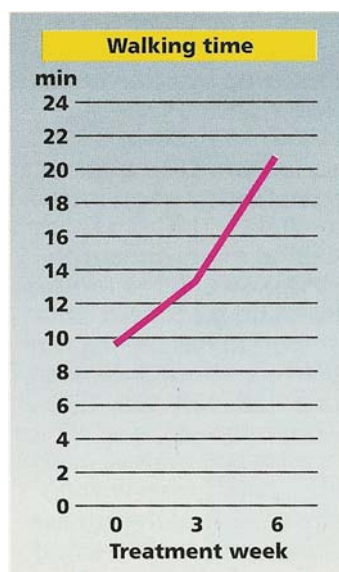
Group of disease	N	Resting blood flow				reactive hyperaemia				statist.	
		before \bar{x}_1	after \bar{x}_2	Δ $\bar{x}_2 - \bar{x}_1$	Δ in % of before	before \bar{x}_1	after \bar{x}_2	Δ $\bar{x}_2 - \bar{x}_1$	Δ in % of before	rest. bl. fl. p	react. hyp. p
	n	ml	ml	ml	%	ml	ml	ml	%	n	n
normal	5	2.3	2.6	0.3	13	32.4	33.5	1.1	3.4	0.01	0.005
I + II	10	1.5	1.75	0.25	16.7	21.7	24.2	2.5	11.5	0.02	0.005
III + IV	10	0.9	1.12	0.22	23.2	13.8	15.7	2.9	21.0	0.001	0.001

Effect of EPL on the muscle blood flow in the lower extremities. Mean values before and after EPL therapy (1,8 g/d per os for 30 days) and their difference are presented.

During the first 2 weeks the patients received 1g/d of intravenous EPL plus 1.35 g orally for another 6 weeks and a subsequent maintenance therapy on 1.35 g/d of oral EPL covering 18 months. An improvement of the oscillometric index and the walking distance (from 0-200 m to 1500 m) was observed in 35 patients. The withdrawal of EPL resulted in a shortened walking distance.

In a crossover trial H. Pristautz (149) investigated the influence of high doses of EPL (1,8 g/d orally) on rheographic and oscillographic findings as compared with the influence of low doses of EPL (1.05 g/d orally) and placebo. A dose – related, distinct increase in the oscillographic index (>0.8 mV) indicated improved vascular passage. Rheographic findings also were characterized by a dose-related improvement. For instance a clear decrease in vessel wall rigidity was observed under the high doses of EPL together with a marked increase in flow rate. The age of the patients was of no account for these findings.

In a comprehensive trial involving 808 patients G. Hevelke et al. (115) confirmed the above results. After a 6-week treatment with EPL, 198 patients with intermittent claudication and 505 with pain at rest reported complete relief. Mean pain-free walking time was extended from 9.8 to 21.3 min on average. About one-third of the patients showed improved pulse recordings. According to the authors the therapeutic success of EPL in impaired peripheral circulation largely depends on its long-term administration.



Mean walking time in min of patients (n=282) before and during treatment with EPL or 6 weeks.

7.9 The Use of EPL in Fat Embolism

According to P. Lawin et al. (194) fat embolism constitutes a variation of posttraumatic shock. It is mostly seen after multiple injuries involving fractures of the long bones, craniocerebral injury or extensive soft-tissue injuries as well as after orthopedic surgery (a.o. osteosynthesis).

In connection with multiple trauma a shock-induced disturbance of phosphatide synthesis is thought to be at the root of lipid de-emulsification, enlargement of fat droplets and obstruction of peripheral pulmonary vessels (pulmonary fat embolism). When fat embolism involves the systemic circulation, cerebral symptoms predominate (cerebral form).

In shock conditions, fat emulsification is strongly improved by intravenous administration of EPL. Being a surfactant, EPL represents a physiological emulsifier.

Clinical experience with EPL in the prophylaxis and treatment of fat embolism has been gathered for about 4 decades (a.o. 128, 129, 145, 157). Within the scope of clinical trials approximately 7000 patients have been treated with high doses of EPL infusions.

When summarizing the clinical (as well as preclinical) results, it becomes obvious that EPL increases considerably the survival rate in fat embolism if the preparation is given early enough, i.e. if it is administered prophylactically in the case of a risk for fat embolism.

Thus, apart from manifestations in the lung also the mostly irreversible cerebral lesions may be prevented.

Lawin et al. (194) recommended to start prophylactic treatment with EPL solution (40 to 50 ml/d for 4 to 5 days) directly on admission of a patient with multiple injuries.

Where signs of fat embolism have already been diagnosed, the daily dosage is to be increased to at least 80 ml EPL and therapy is to be continued until the symptoms of shock have disappeared.



Pulmonary fat embolism

7.10 Tolerance

Clinical trials have shown EPL to be very well tolerated. What is more, no serious adverse reactions have become known from long-term studies over 2 years and us over 50 years.

In isolated cases slight gastro-intestinal complaints like soft stools, diarrhea, constipation, lack of appetite have been observed in patients.

Sensations of heat or flush with or without circulatory reactions have been described following intravenous application. This indicates that contrary to the product recommendations, it has been injected too fast in obviously sensitive patients.

Since the nicotinic acid and AMP has been removed from the formula, these flushes no longer occur as often.

Patients with low body weight and especially Asian and Indian patients have shown reactions of extreme tiredness after intravenous treatment. In such patients, the recommended dose is lower (about half of the regular dose).

Irritations of the vascular walls of veins and their respective symptoms may be provoked if the infusion procedures are not followed correctly, eg. infusion time too short, DW5 or glucose 5% in too small amounts, the use of the wrong catheter.

The investigational reports available make it clear that the number of adverse reactions following intravenous or oral administration of EPL is negligible when compared with the total number patients treated.

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