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Dermatologic Aspects of Hyperlipoproteinemia*

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Clinical and experimental research in the field of hyperlipoproteinemias has made great progress in the last few years. The theme of my todays paper has been chosen to demonstrate the impressively close relationship between progress in natural sciences and progress in medicine. This becomes also evident in the change of names of those diseases which we are going to discuss today.

In the introduction to my paper it may be worthwhile to review some ***historical milestones*** in the development of our knowledge of the familial hyperlipoproteinemias. For the first time in 1835 "Plaques jaunatres des paupieres" were described by Rayer in Paris. Today we know, that these lesions were xanthelasmas. In 1851 Addison and Gull in London gave first appropriate description of the different types of xanthomas. They called these lesions "vitiligoidea", and pointed out already that these diseases may be combined with disturbances of the liver function or with diabetes mellitus. The terminus "xanthoma" for the yellow skin tumors was given in 18 69 by the English author Frank Smith. In the "Atlas für Hautkrankheiten" edited by Hebra in the same year we found a very instructive and clear description of this disease. Some years earlier, in 1863, Wilson already introduced the term "xanthelasma" for plain yellow tumors of the skin. Attempts, however, to classify the various types of skin xanthomas and skin xanthelasmas alone on clinical basis did not give any deeper inside in the pathogenesis of the diseases.

Progress in this respect was possible when it was found out, that not only clinical and morphological aspects of the skin tumors but also the type of disturbances of the lipid metabolism of that organism are of primary and essential importance. Therefore it was the first real progress, when the German dermatologists Pick and Pinkus found in 1908, that cholesterol was increased in their patients with xanthomas. Further progress was realized by biochemical studies, made by the German internist Bürger and the dermatologist Otto Grütz, both of which in 1932 described the "Hepato-splenomegale Lipoidose mit Xanthomen der Haut und der Schleimhäute", the well known Bürger-Grütz-disease. Now it has become clear, that xanthomas and xanthomatosis are the morphological equivalents of disturbances in the lipid metabolism in those patients. In this connection it was the most outstanding merit of Thannhauser with his collaborators, in 1938, (Table 1) to give a new and also prognostically important classification of the xanthomatoses based on the analysis of blood lipids. The distinguished normolipemic, hyperlipemic and hypercholest-

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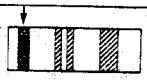
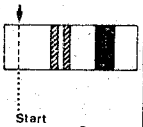
erolemic xanthomatoses in relation to the lipids they found elevated in the blood serum of those patients. Thannhauser already stressed the fact, that in hypercholesterolemic xanthomatoses the serum is clear, whereas in hyperlipemic xanthomatoses the serum is turbid or milky. Since 1950 the intensive studies of Gofman and collaborators have made it clear, that lipids as cholesterol, triglycerides, free fatty acids or phospholipids are not circulating as free compounds in the blood serum, but always in connection with proteins as so called lipoproteins. Since a long time not much has been known about the chemical structure and composition the these lipoproteins, and especially their protein component. In the last years however, it could be shown that there are more distinct protein components which are called apoproteins A, B and C. Perhaps also not yet identified other lipoproteins do exist. All the different lipoproteins seem to be characterized by a typical pattern of the apoproteins.

The modern classification of the different types of hyperlipoproteinemias is based mainly in two methods: namely the measurement of the different density of lipoproteins in the blood plasma using preparative ultracentrifugation and the measurement of the different electrophoretic speed of migration

Table 1. Classification of Xanthomatoses According to Thannhauser

I. HYPERCHOLESTEROLEMIC XANTHOMATOSES
– Primary: Idiopathic fam. hypercholesterol Xanthomatosis
– Secondary: Biliary Liver Cirrhosis. Hepatitis by Arsenic. Congenital Dysplasia of bile ducts
II. HYPERLIPEMIC XANTHOMATOSES
– Primary: Idiopathic hyperlip. Xanthomatosis (Bürger-Grütz)
– Secondary: Diabetes mellitus. Hypothyreosis. Nephrosis. Pancreatitis, v. Gierke's disease
III. NORMOLIPEMIC XANTHOMATOSES

Table 2. Physicochemical Properties of Lipoproteins [LP]

	Size [Å]	Main lipid components	Apo-Lp	Electrophoresis	Ultracentrifugation
Chylomicra	1000 - 10000	Tri 85-90%	A, B, C		d < 0.95 g/ml Sf 400-10^{-5}
Prebeta-Lp	300 - 700	Tri 50% Chol 19%	[A], B, C		VLDL d < 1.00 g/ml Sf 20-400
Beta-Lp	150 - 250	Chol 45%	B, [A]		LDL d 1006-1063 g/ml Sf 0-20
Alpha-Lp	75 - 100	Pholi 30% Prot 50%	A, [B,C]		HDL d 1.013-1.21 g/ml

of the different lipoproteins (using paper electrophoresis).

Generally speaking today four main *classes of lipoproteins* can be distinguished (Table 2):

1. Chylomicrons

These round big particles are floating at a density gradient of 0.095 g/ml. The consist until to 85~90% of exogenous triglycerides.

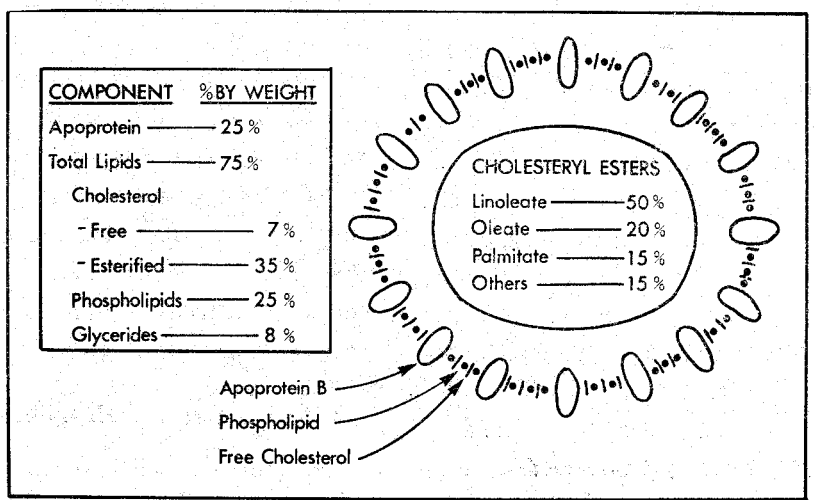
2. Prebetalipoproteins

These are synthesized mainly in the liver. They migrate in the electrophoretic field with the same speed as the alpha 2-globulins. Because of their low optical density they have been designated also as very low density lipoproteins (VLDL). VLDL-particles are much smaller than those of the chylomicrons. They contain about 50% endogenous triglycerides, however also about 20% cholesterol. Therefore they are of importance in their pathogenetic role in arteriosclerotic diseases of the blood vessels. As it seems, they are transformed within the peripheral fat tissue to betalipoproteins.

3. Betalipoproteins

The particles of these lipoproteins are rather small. In the serum electrophoresis they are migrating with the betaglobulines. Because of their lower optical density they have been named also low density lipoproteins (LDL). The LDL-fraction of the blood serum with 45% has the highest content in cholesterol of all plasma lipoproteins. The schematic diagram of Goldstein and Brown (Table 3) shows you the morphological structure of L DL-particles, composed of an apolar core of esterified cholesterol that is surrounded by a polar coat composed of phospholipids, free cholesterol and apoprotein B. These LDL-particles bind to specific receptors on the cell surface of those cells, which are in need of cholesterol for membrane synthesis. We know today, that because of his high content of cholestorol elevated LDL plasma concentrations are atherogenous and infarctogenous. LDL-deriving cholesterolesters will be stored intracellularly.

Table 3. Schematic Diagram Showing the Structure and Composition of Plasma LDL;



According to J.L.Goldstein and M.S.Brown, 1977

4. Alphalipoproteins

These are the smallest of all lipoproteins. They migrate electrophoretically like alpha-globulines. Because of their relatively high optical density they have been named as high density lipoproteins or HDL. They are rich in phospholipids.

Ladies and gentlemen, this classification of lipoproteins is based on the very important investigations of Fredrickson, Levy and Lees since 1965 and of Schettler with Seidel in Heidelberg. One has however to take in mind that these classes of lipoproteins are rather heterogenous, not only in relation to the lipid composition but also in relation to the composition of apolipoproteins. Also, one has to take in account, that we have to do with a biological system, which does not know any definite artificial borders. For example we know, that VLDL is synthesized in the liver, moves to the subcutaneous fat tissue, where the triglycerides are engulfed by fat cells and returns as LDL in the blood stream. So, it does not take wonder, in the same family in different members an increase of different classes of lipoproteins could be observed. This disease has been described by Goldstein et al. as "*multiple lipoproteins type hyperlipidemia*".

Also in the same patient with a given hyperlipoproteinemia under treatment another lipoprotein pattern may develop. This has been noted by Ruffli and Stähelin in 1972, and by Vermeer and Polano in 1975. All those observations seem to teach us that it is not right, to identify a primary type of a hyperlipoproteinemia with one genotype.

Concerning the classification of *primary and secondary hyperlipoproteinemias*, however, the classification which is based on electrophoretic separation of lipoproteins (Fredrickson and collaborators) has been accepted in the definite form given by the WHO. According to this classification, as you know, one distinguishes 6 *types of hyperlipoproteinemias* (Table 4).

Table 4. Types of Hyperlipoproteinemias

Type	
I	Hyperchylomicronemia
IIa	Hyperbetalipoproteinemia
IIb	Hyperbeta- and prebeta-lipoproteinemia
III	"Broadbeta" - Disease
IV	Hyperprebetalipoproteinemia
V	Hyperprebetalipoproteinemia and hyperchylomicronemia

according to FREDRICKSON et al.

Type I-Hyperchylomicronemia

This type is very seldom and identical with the Bürger-Grütz-disease, the lipoidosis with hepato-splenomegaly and xanthomatosis. The triglyceride containing chylomicrones are increased very strongly in the blood serum, especially after exogenous intake of triglycerides. The blood serum is milky and shows a layer of cream after standing. Strongly increased are here the exogenous triglycerides (not seldom until to 10,000mg/ml). Only in this disease we know the etiology, namely a decreased activity of the lipoproteinlipases because of genetical defect.

Type II a-Hyperbetalipoproteinemia

Here the plasma is clear. Increased are only the betalipoproteins or LDL, which are rich in cholesterol. This disease has been

called before "familial hypercholesterolemic xanthomatosis". Triglycerides are not augmental. We know today (on the basis of fibroblast cultures) that in this group we can differentiate between LDL-receptor negative, LDL-receptor defective and LDL-internalize defective forms (Goldstein and Brown, 1977).

Type II b-Hyperbetalipoproteinemia and Hyperprebetalipoproteinemia

The plasma of those patients is clear or turbid. The intensity of the turbidity is in relation to the plasma concentration of endogenous triglycerides in the VLDL-fraction. Also intake of carbohydrates leading to a pathological increase of these lipids.

Type III-Broadbetadisease

This type of hyperlipoproteinemia shows the same optical characteristics as the type II b. Characteristic is a broad beta band in the lipoprotein electrophoresis which in the ultracentrifugation shows the same behaviour as VLDL. This pathological lipoprotein has been named by Polano in 1974 as "beta-VLDL". In all probability it seems to be the result of a disturbance in the physiological metabolic conversion of VLDL to LDL lipoproteins. Cholesterol and triglycerides in plasma are only increased moderately.

Type IV-Hyperprebeta lipoproteinemia

This type is relatively very frequent and a mainly disease of adults. Hyperprebetalipoproteinemia is characterized by increase of VLDL. The increased endogenous triglycerides are mainly produced in the liver. The plasma of those patients is milky but does not show a creamy layer after standing. This hyperlipoproteinemia can be induced by exogenous intake of carbohydrates; very often it is of secondary nature.

Type V-Hyperchylomicronemia and Hyperprebetahyperlipoprotein

We may interprete this type as a combination of the pathological lipoprotein patterns of type I and type IV. Triglycerides are increased rather strongly, cholesterol is increased lightly, the serum is milky and shows a creamy layer after standing. This disturbance has been called in former time as "familial exogenous and endogenous hypertriglyceridemia" or "mixed hyperlipidemia".

One has to know further on, that beside of these primary and familiar hyperlipoproteinemias the same disturbances in the lipoprotein pattern in the blood plasma with clinical consequences can also develop secondarily. Without and doubt, diabetes mellitus, chronic pancreatitis and alcoholism are the most important inducers of secondary hyperlipoproteinemias.

Ladies and gentlemen, *for a dermatologist* who is in practice this classification of hyperlipoproteinemias seems to be rather difficult. We have also to realize, that the electrophoretic lipoprotein pattern are not so specific. Therefore we are justified to ask the question: Do we need all these difficult procedures? And we are happy that we can state: No. What we need is two fold

1. Inspection of the serum, whether the serum is clear, turbid, milky or creamy after standing,

2. Estimation of the concentration of cholesterol and triglycerides in the plasma. With these rather simple methods and the clinical manifestations it is possible to identify about all types of hyperlipoproteinemias beside of the Broadbeta-disease.

Early diagnostic of these diaseases seems to be a very important obligation for all of us. Since hyper-lipoproteinemias show clinical

manifestation not only in the eyes, the heart and in the peripheral vascular system but also not seldom on the skin, every dermatologist should look to those symptoms and should be well acquainted with the general significance of the registered symptoms. In this connection especially the clinical work of Polano should be mentioned. With Polano we can classify *xanthomatous skin lesions* in the following way: xanthelasma palpebrarum, xanthoma planum diffusum, xanthoma tuberosum, xanthoma papuloeruptivum, xanthoma palmare striatum et papulosum and xanthoma tendinosum et articulare. Here some clinical demonstrations:

1. Xanthelasma palpebrarum

This as we know can also develop without a hyperlipoproteinemia. In adults below 40 years, however, in adipose patients and in patients with diabetes mellitus, they should let think on hyperlipoproteinemia as with an increase of the LDL fraction.

2. Xanthoma planum diffusum

Clinically these flat lesions are xanthelasmata corporis. In most cases you do not find a hyperlipoproteinemia, but a combination with paraproteinemia, myeloma, leukemia or malignant lymphoma. Such cases have been studied especially by Winkelmann and Bazex.

3. Xanthoma tuberosum

These yellow brown nodes and tumors are developing slowly. As predilection areas they are to find on loci of pressure, especially elbows and knees. In the blood of such patients one usually finds an increase of the cholesterol-containing LDL-fraction. In homozygote cases of hyperbetalipoproteinemia especially in children you can find also xanthomas on the dorsal parts of the interphalangeal joints, in the gluteal area and in skin folds.

4. Xanthoma eruptivum

Here in short time of weeks papulo-eruptive disseminated xanthomas do develop. Not seldom they show a red halo and are itching. Typical predilection areas are the gluteal area, thighs and palms. They are mainly induced by VLDL or chylomicrons, when triglycerides reach values around 1500mg% and more. After a reduction they incline to spontaneous regression. Sometimes eruptive xanthomas are combined with tuberous xanthomas. Here also the LDL-fraction is elevated.

5. Xanthoma palmare striatum

This lesion is shown in the next slide with a yellow staining of the palmar creases. They are rather typical for the Broad-beta-disease; they can, however, also be found in other types were we have to deal with an increase of the VLDL-fraction as for example in type II b or IV.

6. Xanthoma tendinosum et articulare

Clinically these are subcutaneous nodules and nodes which mainly are to be found on the extensor of hands, feet and on the achilles tendon. They are induced by an increase of the cholesterol-rich LDL-fraction in the blood serum. Therefore they are very typical for type II a-hyperlipoproteinemia, especially in homozygote cases.

In type I and type V they do not occur.

7. Arcus lipoides corneae

Also the dermatologist should look into the eyes of his patients. In all cases where you find an arcus lipoides below the 40 year of life, there is a suggestion for a hyperlipoproteinemia. Very typical is the sickle shaped gerontoxon juvenile for type IIa-hyperli-

poproteinemia. It can however also be observed in cases with an increase of the LDL-fraction as in type IIb or in about 20% of the cases of type III.

What can we conclude from these observations? In fact, special types of xanthomatous lesions point to an increase of special fractions of lipoproteins as it is shown in the next slide (Table 5). It seems, however,

Table 5. Xanthomas as Skin Markers of Hyperlipoproteinemias

Skin lesions	indicating increased		
	Lipids	Lipoproteins (Lp)	Density of Lp
Xanthelasma Xanthoma planum diffusum Xanthoma tuberosum Xanthoma tendinosum	cholesterol	beta - Lp	LDL
Xanthoma eruptivum	triglycerides	chylomicra prebeta - Lp	VLDL
Xanthoma palmare striatum	triglycerides	prebeta - Lp broadbeta - Lp	VLDL

that the skin manifestations in hyperlipoproteinemias are not in a very strong relation to the special types of hyperlipoproteinemia. Together with Polano also in our experience, in type IIa never papuloeruptive xanthomas do occur –, and in type IV never xanthelasmas, tuberous xanthomas and xanthomas of the tendons or joints. But the question, why an increase of the LDL-fraction induces the development of an arcus lipoides corneae, xanthelasmas, tuberous xanthomas or xanthomas of the joints and why an increase of the VLDL-fraction in the blood induces eruptive xanthomas, is not yet clear until today. It seems, that excessive amounts of VLDL will be taken up by cells of the macrophagocytic system very rapidly.

The investigation of the ***pathogenesis of xanthomatous lestons*** in hyperlipoproteinemia seems important, because as also pointed out by Parker, from those investigations conclusions can be drawn in relation to the pathogenesis of atherosclerosis.

The ***histological substrate*** of all types of xanthelasmas and xanthomas in all different types of hyperlipoproteinemias is characterized by the formation of foam cells and foam giant cells(Fig. 1). The foamy cytoplasma of these cells is caused by the dissolution of lipids during the histological embedding procedure. In xanthelasmas one finds mostly more sharply demarcated collections of bigger foam cells, whereas in hyperlipidemic xanthomas as in type II b-, type III- and type IV-hyperlipoproteinemia a more diffuse infiltration of the dermal tissue by smaller not very well demarkated foam cells prevails. It is, however, not possible on the basis of histological investigation of a given xanthoma to conclude, what kind of hyperlipoproteinemia the patient does suffer.

Also the ***chemical lipid composition*** of xanthomas shows, that all types of lipids are to be found in xanthomas and that the composition is not in a stronger relation to a type of hyperlipoproteinemia in the same patient. We know only that the chemical lipid composition of very young developing xanthomas is rather similar to the lipid pattern in the blood serum. This seems, that lipoproteins will undergo further transformation. Also using histochemical methods one can show that all types of lipids as: cholesterol, cholesterolesters, triglycerides, fatty acids and phospholipids are present in xanthomas of different origin. In the next figure (Fig. 2) you can see on the upper side a Sudan black stain for lipids and on the lower the same section under partly polarized light with many cholesterol crystals. From own investigations we know that also the lipid composition within foam cells does change also with ageing of foam cells. In small foam cells we can find much more trigly-

cerides as in older foam cells.

What do we know about *morphogenesis of xanthomas?* Many years ago, Gottron has pointed out already, that accumulation of cells preceeds the lipid storage. This seems to be true. Especially in the lateral parts of xanthomas or xanthelasmas you can find an accumulation of lymphocytoid or histiocytoid mononuclear cells which are located in the perivascular space or without any relation to blood vessels within the dermal compartment (Fig. 3). Already in those cells, using histochemical methods, lipids can be demonstrated in very small amounts. We have called these cells "foam cells type 1". From where these cells are coming? We tried using ^{3}H-thymidine as a marker of cells in the DNA-synthesis to elaborate the question whether the accumulation of those cells is caused by local proliferation or just by accumulation. You can find mononuclear cells which are marked by the incorporation of ^{3}H-thymidine during the DNA-synthesis phase. However, we could never find DNA-synthesis or mitoses in mature foam cells. This let us conclude, that the lympho-or histiocytoid cells at least to a part also can be produced in the skin itself. In all probability however, also macrophages (monocytes) of the blood are able to take up lipoproteins and to form foam cells and foam giant cells.

Since years many authors have raised the question about the *origin of xanthoma foam cells* (Table 6). Already in 1913–14 the Russian author Anitschkow brought up the suggestion that xanthoma cells are perhaps nothing else than blood-and tissue macrophages which have a engulfed great amounts of lipids. Meanwhile this suggestion could be proven by histochemical and electronmicroscopical investigations. The cytochemical pattern of enzymes in lymphocytoid and histocytoid cells and in foam cells of different xanthomas is uniform and it shows, that all those cells are macrophages in different stages of their development and, that all these cells have a functionating lysosomal enzyme system. These cells have a rather strong metabolic activity. These macrophagic cells furtheron, show a strong positive cytochemical reaction for acid phosphatases, nonspecific esterases, leucine aminopeptidase. Also single cells show a strong lysosomal enzyme (Fig. 4) and you can detect that as smaller the cells, as more intensive are the histochemical reaction. From these investigations (Table 7)

Table 6. Origin of Xanthoma foam Cells

Author	Year	Suggestion
TÖRÖK	1893	Embryonic fat cells
GEYER	1897	Lymphatic endothelial cells
PICK - PINKUS	1908/10	Connective tissue cell
ASCHOFF	1910/13	Reticulum cells
POLLITZER - UNNA	1910/14	Degenerated myofibrils
ANITSCHKOW	1913/14	Blood and tissue macrophages
CORTEN	1920	Any immature cells
PETRI	1923	Vascular endothelial cells

According to E. URBACH, (1932)

Table 7. Cytochemistry of Foam Cells

enzymes	initial foam cells	old foam cells
nonspec. esterases	+++	++
acid phosphatases	+++	+/++
N-A-S-D-acetate-esterase	+/++	+
leucine amino peptidase	+++	++
peroxidase	ø	ø

Conclusion: The cytochemical enzyme pottern of foam cell and macrophages is identical

we can conclude, that the cytochemical enzyme pattern of foam cells and macrophages is identical. Foam cells are very active cells which have a well functionating lysosomal enzyme system. Also electromicroscopical in-

vestigations are in good agreemant with these results, as also shown by the excellent work of Parker and Oldland. Already on a semithin section one gets an impression of the close neighbourhood of blood vessels and xanthoma cells. One sees tissue macrophages with only a few vacuoles(foam cells type 1) and typical foam cells (foam cells type 2) with many vacuoles in an onion-shaped arrangement around the blood vessels. Sometimes (Fig. 5) endocytosis of blood serum and greater amounts of lipoproteins in between endothelial cells and their basal lamina could be found. We do not know until now, however, how lipoproteins permeate the vessel wall and whether they will be changed chemically or physicochemically during the process of passing the endothelial cells. There is no question, however, that lipoproteins have to penetrate the vesselwall. This has been shown using immunopathological methods. In xanthomatous lesions smaller blood vessels with a strong yellow fluorescence indicating LDL-deposits could be found. We were able to demonstrate using immunohistochemical methods also lipoproteins within the xanthomatous lesions. The changes of lipoproteins passing the endothelial wall have to be relatively mild.

Perithelial cells do engulf lipoproteins and are capable to form foam cells. On the next slide (Table 8) you will see, that lipoproteins are intracellular droplets or vacuoles, triglycerides are empty vacuoles because they are metabolized very fast. Cholesterol is dissolved during the preparation; therefore you see free spaces. Free cholesterol, however, should form with digitonine cholesterol-digitonine-complexes, which are demonstrable as cylindric needles. Phosphatides form membranes and myelin-like figures.

Table 8. Chemical Morphology of Foam Cells

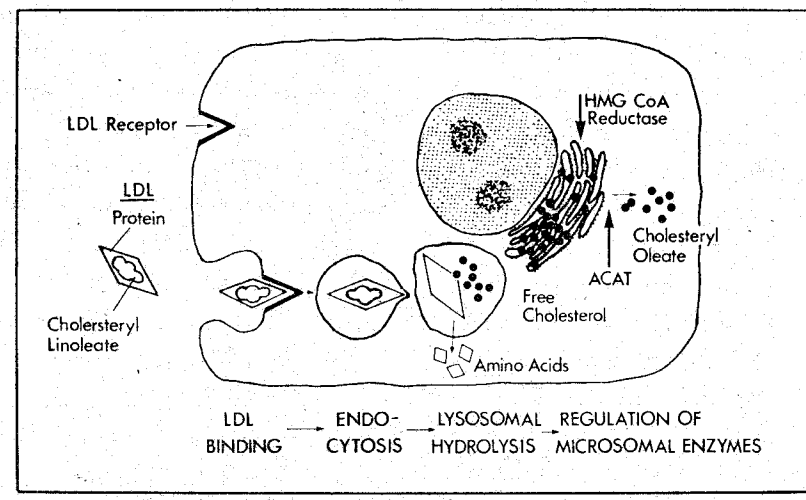
Chemical Substrate	Ultrastructure
LIPOPROTEINS	Droplets with content
TRIGLYCERIDES	Empty droplets or vacuoles
FREE CHOLESTEROL	Empty clefts
DIGITONIN CHOLESTEROL	Electron-opaque 'spicules' and needles
CHOLESTEROL ESTERS	None
PHOSPHATIDES	Membranes, lamellate bodies or myelin figures

In early foam cell formation, the phagocytic cells are filled with multiple vacuoles which contain some electrondense material, probably blood lipoproteins (Fig. 6). In older foam cells these vacuoles are empty, and there is an increase of cholesterol crystals, phosphatid-containing membranes and phagosomes. In the next slide (Fig. 7) you see beneath a blood vessel a foam cell with empty vacuoles and multiple electrondense phagosomes. Using an acid phosphatase reaction for electronmicroscopic demonstration we could see dense precipitates within these secondary lysosomes.

These investigations show, that foam cells are nothing else than macrophages, which do engulf lipoproteins and are involved in the processes of degradation and transformation of lipoproteins. They are, therefore, active cells, which do not only storage the phagocytized lipoproteins.

Newer investigations have shown, that *LDL is probably the most important lipoprotein in the development of xanthomas.* Under experimental conditions the LDL pathway has been detected by Goldstein and Brown (Table 9). When cells are in need for cholesterol, they synthesize specific receptors, that become localized to the cell surface. Those receptors could be shown on an ultrastructural basis. LDL binds to these receptors

Table 9. Sequential Steps in the LDL Pathway in Cultured Human Fibroblasts



According to J.L. Goldstein and M.S. Brown, 1977

with high affinity, and the bound LDL is taken up by a process which resembles adsorptive endocytosis. The endocytic vesicle then migrates to the lysosomal region of the cells, where the lipoproteins will be degraded. The protein of LDL is hydrolized by lysosomal proteases to amino acids. The cholesterol esters of LDL are hydrolized by a lysosomal acid lipase. Having obtained cholesterol from LDL, the cell how suppresses its own cholesterol synthesis by inhibiting a HMG-CoA-reductase activity. This leads to a decrease of the intracellular cholesterol synthesis. Homozygotes of familial betalipoproteinemia mainly are LDL receptor negative or receptor-defective. Therefore, LDL is accumulated extracellularly in the blood and hyperbetalipoproteinemia (hypercholesterolemia) does develop. The consequence on the intracellular level is: lacking inhibition of the endogenous synthesis of cholesterol and therefore a intracellular cholesterol overproduction. The increased amounts of LDL in the extracellular space of the human body will be taken up mainly by macrophages giving rise to a formation of foam cells.

It is not yet known, what the determinant factors are the clinical *localization of xanthomas* in a given skin area. We know from clinical observations, that xanthomas especially in cases of betahyperlipoproteinemia do develop mainly in regions, where the skin is exposed to mechanical traumas as on the elbows, knees or in scars. Also, the development of skin lesions is to be observed within other skin lesions. For example, we could see in one case of hyperlipoproteinemia of type IV, in a patient with psoriasis xanthomatous lesions within psoriatic lesions. Especially Walton and his group did make interesting animal experiments to look what kind of tissue factors could be of importance in the localization of xanthomas in hyperlipoproteinemias. We also have done some experiments in albino rabbits. We induced a hypercholesterolemia using a diet with 2% cholesterol. The blood shows great amounts of granular black stained lipoproteins. After 4 to 6 weeks we could see a spontaneous development of xanthomas which also from a point of histopathology were very similar to those in human xanthomas. Within blood

vessels and in the perivascular tissue sudanophilic lipoproteins can be detected which can be shown in polarized light to contain greater amounts of double refractlie cholesterol crystals. It was possible by induction of local disturbances within the skin to induce macroscopic xanthoma formation in these places. As you see from (Table 10) xanthoma

Table 10. Experimental Xanthoma Formation in Rabbits

METHOD		XANTHOMA-FORMATION	
		macroscopic	microscopic
hyaluronidase	i.c.	+++	++
trypsin	i.c.	++	++
bromelin	i.c.	+	+
croton oil	e.c.	+	++
incision	i.c.	0/+	+(+)
NaCl	i.c.	0	+

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formation could be induced by injection of mucolytic or proteolytic enzymes or by induction of a stronger inflammation. Also after incision xanthoma formation could be observed three months later. 8 days after a histamine injection histological xanthomatization could be detected. Such results lead to the conclusion, that in the process of development and localization of xanthomas also local factors may be of great importance. Interestingly enough, also here macrophages are involved whereas other cells in the skin as for example fibroblasts never showed transformation in foam cells because their metabolism was not altered. This leads to the suggestion that when the plasma LDL level rises, macrophagic systems are involved to lower these concentrations. This mechanism is very important in the development of atherosclerosis.

Table 11. Pathodynamics of Foam cell Formation in Hyper-lipoproteinemias

CIRCULATION

Pathological concentration of lipoproteins

VESSELS

Abnormal vascular permeability

Abnormal lipoproteinlipase activity

Penetration of lipoproteins through vessels

CONNECTIVE TISSUE

Deposition of ß-lipoprotein containing lipoproteins

Accumulation (proliferation ?) of macrophages

CELLS

Incorporation of lipoproteins within pericytes and macrophages

FOAM CELLS

Desintegration of lipoproteins by proteolytic and lipolytic enzymes

CHOLESTEROL — Deposition of crystals of free cholesterol
CHOLESTEROL — Re- or transesterification of cholesterol

PHOSPHATIDES — Deposition (or new formation) in phagosomes or myelin figures

TRIGLYCERIDES — Hydrolysis

Further exchange with the surrounding tissue

What are the conclusions(Table 11) which can be drwan from newer observations concerning the formation of xanthomatous lesions?

1. Lipoproteins are increased in the plasma of those patients.

2. The lipoproteins have to penetrate through the walls of blood vessels to reach the perivascular tissue. According to our investi gations permeation of lipoproteins through endothelial cells does occur without any greater degradation or transformation. Under experimental conditions it could be shown, that disturbances of the vascular permeability, of the vascular width, perhaps also of the vascular lipoprotein lipase activity are factors which are of importance in the development of xanthomatous lesions in the skin.

3. Extracellular deposits of plasma lipoproteins especially of LDL fraction are inducing cellular reactions. The consequence is an accumulation of lymphocytoid or histiocytoid macrophages. Lipoproteins are engulfed by these cells and also by pericytes which then do transform in foam cells or foam giant cells.

4. I could be shown that foam cells are not only the result of a simple process of an engulfment and of storage of lipoproteins. Foam cells do have an intact lysosomal system, where lipoproteins can be degraded and also be transformed. Therefore, according to the type of hyperlipoproteinemia and also to the type of hyperlipoproteinemia and also to the age of foam cells, differences in the intracellular enzyme pattern and in the quality of lipids are to be observed. With an increase of the cellular deposits of cholesterol and phospholipids, the lysosomal activity of the macrophagic foam cells decreases. From all these investigations we can conclude, that tissue macrophages in different phases of their development and their phagocytic activity are the typical cellular substrates of xanthelasmas and xanthomas. We can also speculate that in the pathogenic process of atherosclerosis this type of reaction does play an important role.

The dermatologist has rather often the great advantage to see skin lesions which point to internal disturbances. I would like to end my talk with the recommendation that the dermatologist in clinic and practice should always look for xanthelasmas, xanthomas and arcus lipoides corneae and should be aware, that such typical formations may be induced by a hyperlipo-proteinemia. By his diagnosis he may be able to contribute to early treatment and, therefore, to a better prognosis of the disease in his patients. Beside all this, also the investigation of skin lesions using modern methods of natural sciences can contribute to a better understanding of pathological processes which may also develop in other organs or systems of the body.

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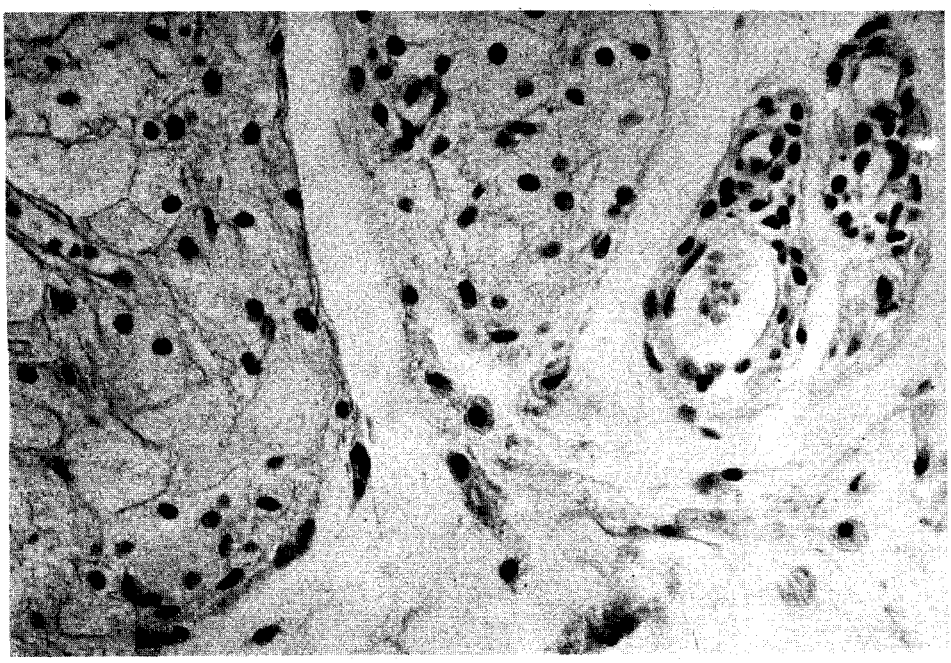

Fig. 1. Xanthelasma. Many foam cells and foam giant cells. Hematoxilin-Eosin.

Fig. 2. Xanthelasma.
a. Sudan black stained lipids in foam cells and foam giant cells.

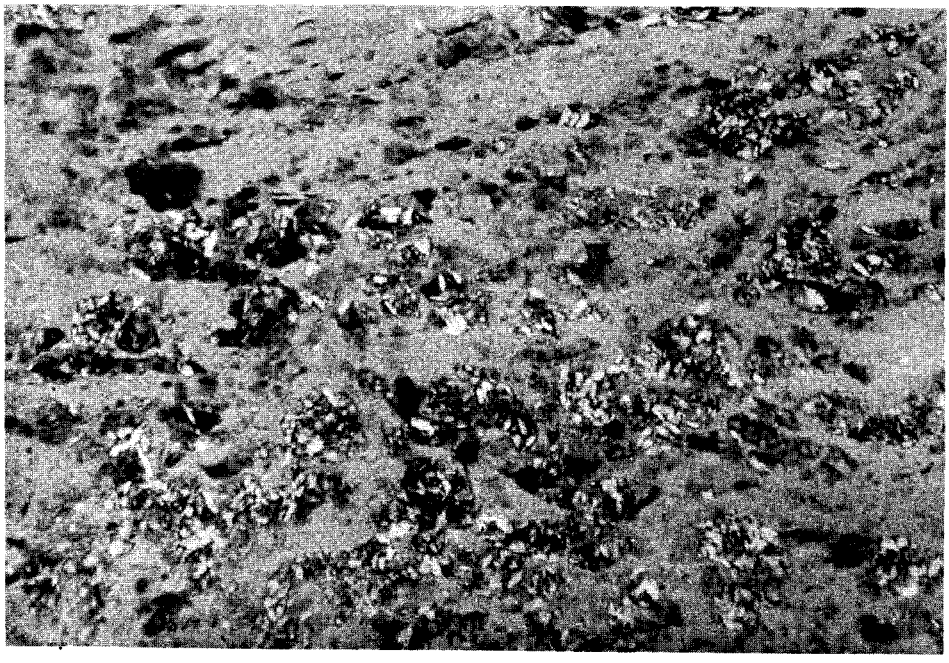

Fig. 2. Xanthelasma.

b. The same in 50% polarized light, showing double refractile.

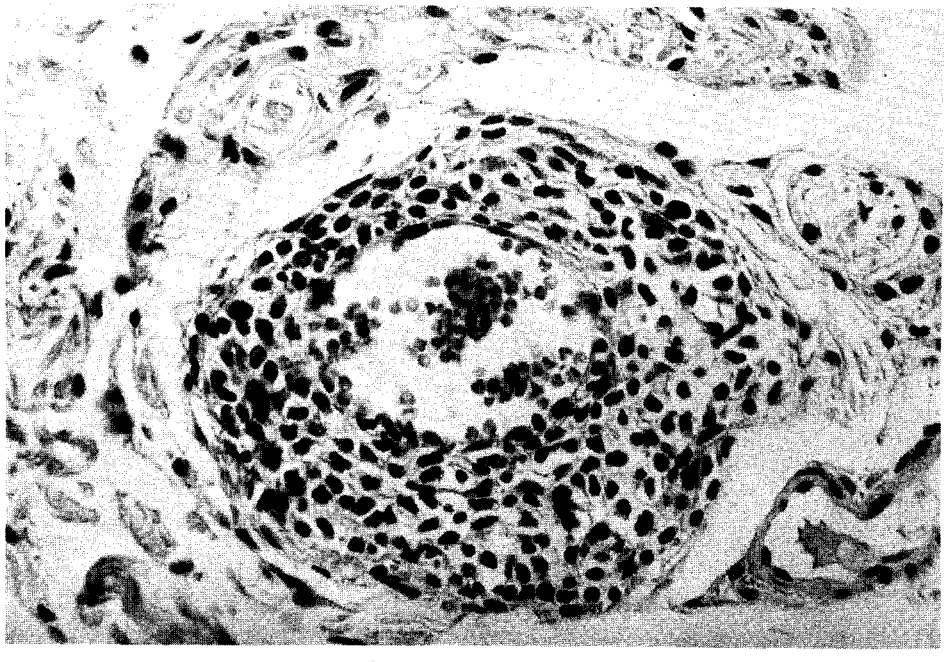

Fig. 3. Xanthoma. Accumulation of lymphocytoid or histiocytoid cells (foam cells, Type I) in the perivascular area.

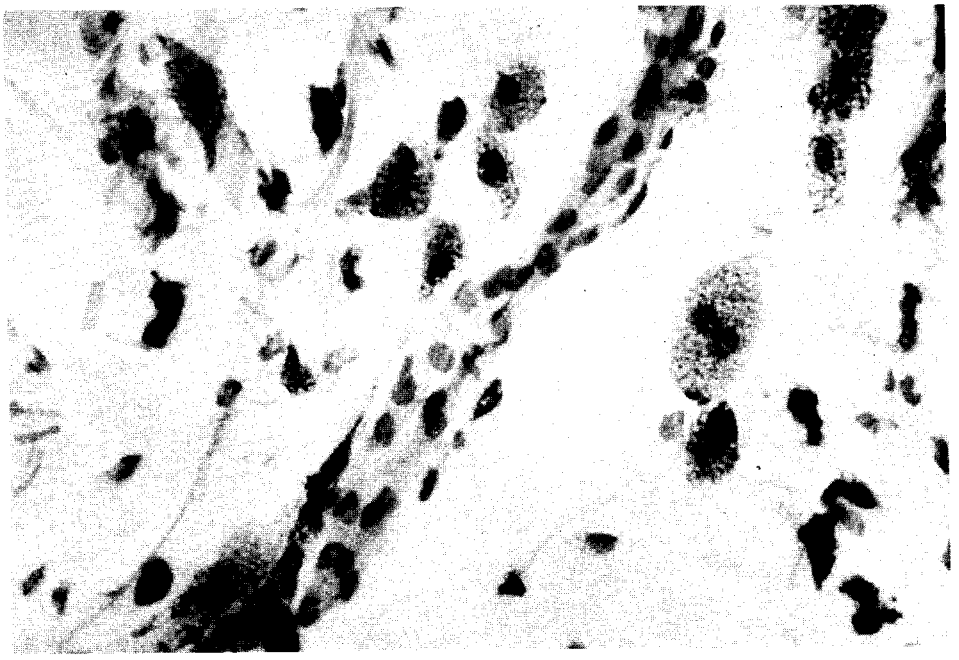

Fig. 4. Xanthelasma. Single xanthoma foam cells with rather strong activity of α-naphthyl esterase.

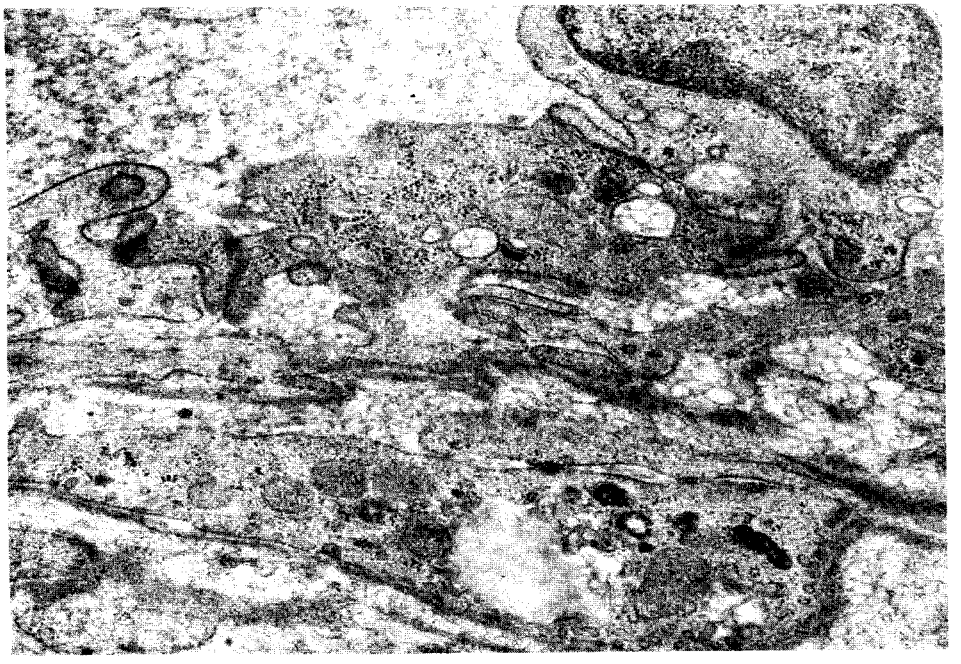

Fig. 5. Endocytosis of blood serum within an endothelial cell and within a perithelial cell as well as in the area of the basal lamina
Left upper part: Lumen of the blood vessel. 38,800.

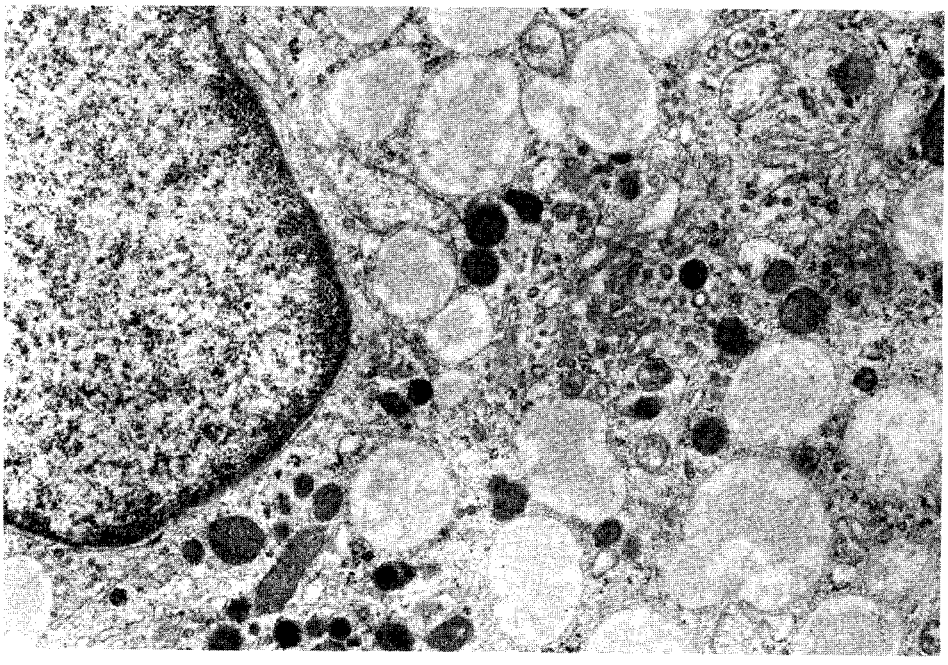

Fig. 6. Ultrastructure of a early foam cell: Phagocytic cell with a well developed Golgi complex and many small dense bodies multiple vacuoles with low electron-dense material, probably blood lipoproteins. 26,000.

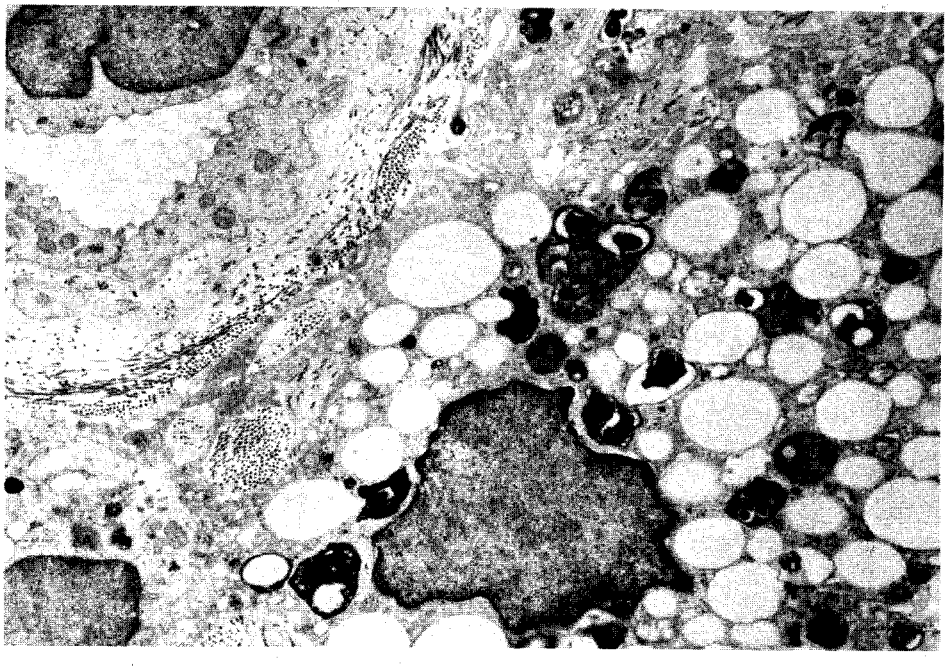

Fig. 7. Ultrastructure of a older foam cell. In the upper right a capillary. The foam cell shows a many empty vacuoles, and rather electron dense phagosomes with a phosphatidcontaining membranes.