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## ORIGINAL CONTRIBUTIONS

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# Protein transport and protein storage in etiology and pathogenesis of arteriosclerosis

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With 17 figures and 7 tables

(Received June 30, 1980)

### Physiology of protein transport and storage in man

According to a speech held on the "10th International Conference on Health Education", London, Kings College, September 2nd, 1979.

*The problem*

According to the now valid doctrine of nutrition, man and other mammalia do not possess a protein store (S. M. Rapoport, 1969). Surplus protein of overnutrition is burned down. Even total meat-food, lifelong, goes together with good health, as Esquimaux demonstrate (H. Glatzel, 1976). Regardless in which form the human body takes in calories, the not immediately needed surplus is stored as fat (Errol B. Marliss, 1978) in subcutaneous tissues, leading to obesity and, for reasons yet unknown, to risk factors and arteriosclerosis. If, however, the patient loses 10–20 kg fat within a four week's 0 diet, his risk-factors hypertension (J. O. B. Spencer: Lancet, 1968, p. 288), adult diabetes (E. F. Pfeiffer: Periskop, May 10, 1973) and gout (D. P. Mertz: Stuttgart, 1978) lower to normal levels. Therefore fat is considered to be the pathogenic factor of overnutrition (G. Schlierf et al., 1978). We are going to find out whether that deduction of the present doctrine is true.

*The facts about storage*

*Figure 1* shows the microscopical slice of subcutaneous tissue in a normally nourished person. There are collagen fibers, elastic fibers and fat cells. The cavities between the fibers are filled in life with mucopolysaccharide and water.

*Figure 2* shows the subcutaneous tissue of an obese person. Here we see nothing but fat cells. That approves of the present doctrine that overnutrition leads to obesity. If, however, we examine subcutaneous tissue in the same fat person at another spot (Fig. 3), we see nothing but collagen fibers. But collagen is pure protein. Overnutrition with mixed food, therefore, increases not only fat tissue, but also protein tissue.

*Figure 4* is tissue of omentum majus from a normally nourished man. There are collagen fibers and a filled fat cell. Let us examine now the consequences of hunger:

*Figure 5* shows the tissue of omentum majus from a healthy rabbit which died of hunger. In this picture, the fat cells are empty, there are no collagen fibers at all, between elastic fibers are large empty spaces. That demonstrates that hunger empties not only the fat cells, but consumes also the whole collagen content of tissues.

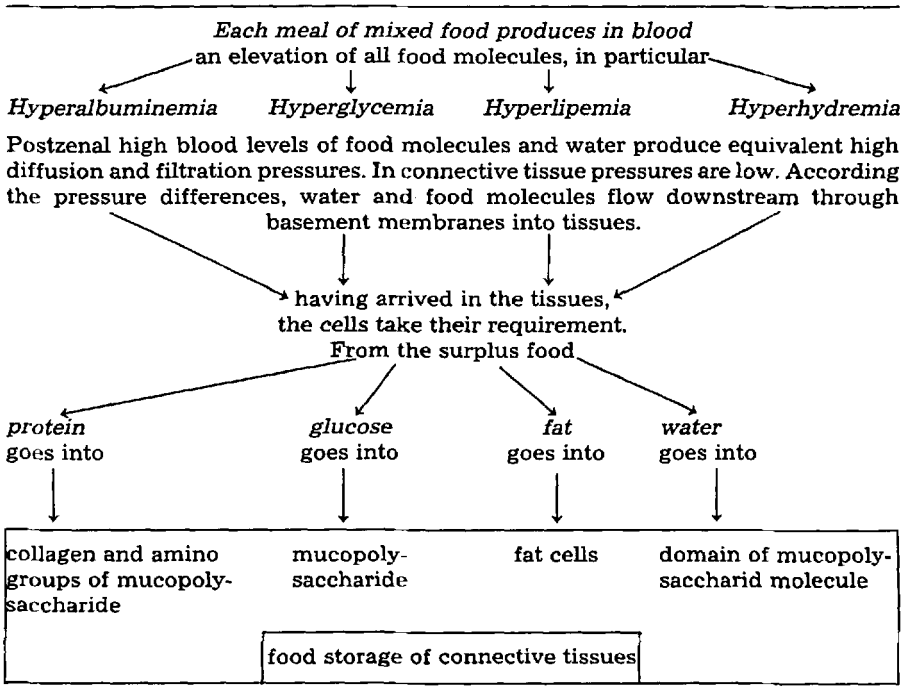
*The foodstore of the body*

The filling of fat cells in overnutrition and their emptying in hunger is explained by the present doctrine with the function of a fat store (F. A. Gries et al., 1977). The same behaviour of the collagen fibers, however, is not taken notice of. Instead, the present doctrine claims man and mammalia do not possess a protein store. That is illogical. The present doctrine is wrong in this respect; it needs correction. After what we have seen on the pictures, it is obvious that the subcutaneous and interstitial tissues store also protein and not only fat. But that is not all. Connective tissue contains – apart from a third of the whole protein content of the body (P. Gedigk, 1974), approximately 8 kg, and a half of the total fat of the body (F. A. Gries et al., 1977) – also a third of the water content of the body (H. Eppinger, 1949) and about the same amount of carbohydrates, which are stored in the mucopolysaccharide molecule. The latter could not yet be measured accurately on account of methodical difficulties, but approximately it has the same storing capacity as the other storing-molecules. That indicates: subcutaneous and interstitial tissues are the main foodstore for all food molecules (Table 1).

*The physiological transportation and storage of food molecules in overnutrition with mixed food according to our doctrine (Table 1)*

Our food is split up by digestion into water-soluble molecules. After resorption by the bowels, the food molecules are transported through the liver into the blood circulation, the carbohydrates as glucose, the fat as fatty acids and lipoproteins, the protein as amino acids and albumin. Every meal of a mixed food increases the food molecules in the blood, leading to hyperalbuminemia, hyperglykemia, hyperlipemia, hyperhydremia. The high blood levels of food molecules produce accordingly high diffusion pressures, by which the food molecules are pressed through

Table 1. Physiological storage in overnutrition according to our doctrine




This process of food metabolization and storage has lowered the filtration and diffusion pressures in blood and tissues to normal, has equalized the pressure differences. The metabolism has attained again its zero state of rest. This metabolization of an hypercaloric meal is only possible under the cooperation of a tissue store with a specific storing molecule for each food molecule.
The assumption of the present valid doctrine that all surplus food is stored as fat could not explain the multiplication of all storing molecules in subcutaneous tissue in overnutrition and their fading in hunger.

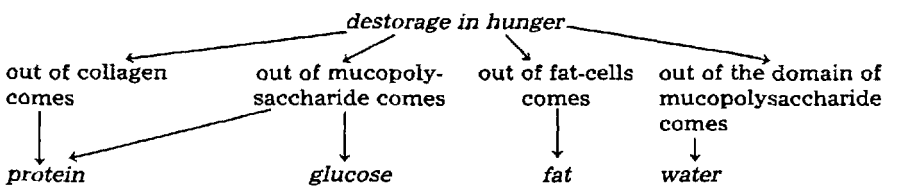



Table 1 is only an example of the structure and function of the tissue store for food molecules. In reality it is much larger with many more storing molecules: Calcium in the bone, iron in Kupffer's cells of the liver, iodine in the tissue of thyroid gland and many more.

basement membranes. Arrived in the tissues, the food molecules are resorbed by the cells, the surplus is stored, the albumin as collagen and as amino group of mucopolysaccharide, glucose as mucopolysaccharide, fat as triglyceride in the fat cells, water in the mucopolysaccharide. So each of

the 4 foodstuffs is stored in its own specific storing molecule in connective tissue.

## The functions of the tissue store

If one speaks of a food store, one usually thinks of its function in times of hunger. But the tissue store is in times of surplus food even more important than in times of hunger.

In overnutrition, more food molecules arrive in the tissues than the cells demand. If the surplus food molecules would stay in tissue fluid, each hypercaloric meal would increase the number of surplus food molecules in tissues. But with their encreasing number, the diffusion pressure grows which they effect. With increasing tissue-diffusion pressure, however, the pressure differences against the postcenal diffusion pressures in capillary blood diminish and ultimately disappear completely. Without pressure differences between the capillary blood and the tissue fluid, the transport of food molecules from capillary blood to tissues stops. That would mean death in a few days. To prevent it, surplus food molecules in tissue fluids which are not resorbed from the cells must be changed in a molecular form which produces no diffusion pressure. That molecular form is the water-unsoluble storing molecule, which produces almost no diffusion pressure. It is metabolically inactive. To change surplus molecules into metabolical inactivity, the existence of a storage molecule for each food molecule in connective tissues is of vital importance.

### *About storage molecules in subcutaneous and connective tissue*

Storage molecules are unsoluble in water. Thereby they are chemically and metabolically inactive and storable.

*Fat* is stored as water-unsoluble triglyceride in the fat cells of subcutaneous tissues. For transportation it is changed by dehydration into water-soluble glycerin and fatty acids.

*Carbohydrates* are stored in two different molecules, glycogen, a pure polysaccharide and mucopolysaccharide, an aminosugar. The glycogen is located in liver, kidneys and muscle cells, the mucopolysaccharide in connective tissue and basement membranes of blood vessels. The sugar content of mucopolysaccharide store is conspicuously larger than that of the glycogen store, which suffices only from meal to meal. The building up of glucose to glycogen depends on insulin, the building up of mucopolysaccharide is independent of insulin.

*Water* appears in the body in two forms, as active, hydrodynamic water and as inactive, stored water. Active water functions as transportation means extracellularly and as reaction part intracellularly. Inactive water is stored between the fibres of the mucopolysaccharide molecule and in its domain (Figure 6).

*The mucopolysaccharide molecule* is not compact, but open at its outside. Thereby it can extend its storing power for some distance into its surrounding. That surrounding is called its domain. The water in the mucopolysaccharide and in its domain is stored, that means immobilized, bound to the mucopolysaccharide. The stored water neither can mix itself

with the water of the tissue stream, nor can other molecules – for instance glucose or oxygen – use the stored water for transportation by flowing through the molecule. On the contrary, in the storage state the water is inpenetrable for flowing water and for all other molecules. Stored water cannot mix itself with passing flowing water. Therefore too much mucopolysaccharide, stored in the tissues, can become a hindrance to the flowing water of the tissue stream, endangering the cell supply.

The mucopolysaccharide is evolutionarily the oldest storage molecule of the multicellulars. It lies extracellularly, somewhat primitively in amorphic masses between the cells. Its building up and breaking down occurs by most simple synthesis and hydrolysis without a complicated enzyme spectrum. It needs no insulin. It stores sugar, protein ($NH_2$) fat and water in one molecule. All those particulars characterize the molecule as belonging to a very early phase of evolution.

The intracellular storage of glucose as glycogen in liver and muscle cells, the intracellular storage of fatty acids as triglyceride in specified fat cells of connective tissues, and the intracellular storage of protein in form of enzyme multiplication was developed at a much later date in evolution, when specific storing cells and specified enzymes, in particular insulin, for building up and breaking down the storing molecule were developed.

As storage and destorage of the foodstuffs "sugar, protein, fat and water" is easily performed with mucopolysaccharide, and as it is most near to all cells, this molecule is used in the first place for storage or for distribution according to cellular want.

Mucopolysaccharide, however, is an amino-sugar molecule. How can it store protein? The explanation is simple: Endogenous protein synthesis can occur if enough amino acids are available. Endogenous amino-acid synthesis can occur if two conditions are fulfilled,

1. the provision of the C skeleton of amino acids, and
2. the amino group for the transaminization of the C skeleton.

As the C skeleton can be taken from fat metabolism as well as from carbohydrate metabolism, the amino group is the limiting factor of endogenous protein synthesis. Therefore it is sufficient if mucopolysaccharide stores amino groups for protein synthesis.

*Collagen* appears in many different molecular forms in the human body. The reason for this polymorphism is that collagen has to perform, apart from protein-storing, many other functions in the different organs of the body. Therefore even the collagen molecules of connective tissue and basement membrane are different. For the purpose of storing, the polymorphism of collagen is of no importance, but only its protein character.

*The calcium, phosphate, and carbonate store* is the bone, *the iron store* the Kupffer's cells of the liver, evolutionarily both belonging to the mesoderm, like all other storage tissues.

## Food dish and food store

Evolution has set this main store for all nutrition molecules at the optimal place of the body, the connective tissue. By that location, connective tissue can perform its double-function, being hydroculture as well as store for all foodstuffs, in which all cells are swimming. By those qualities

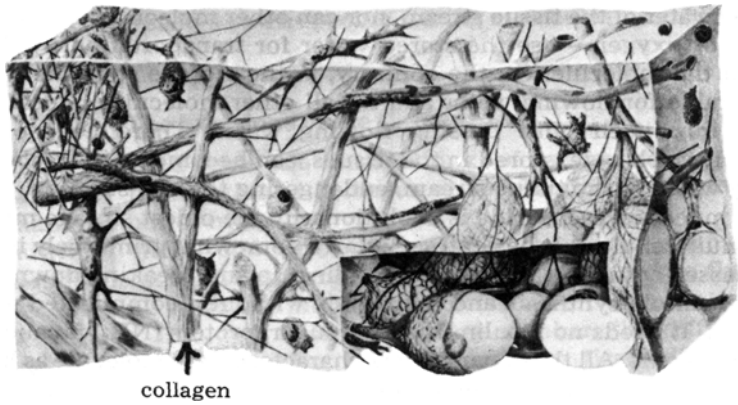



Fig. 1. Normal connective tissue of a normally nourished person. A. Maximow (1927)

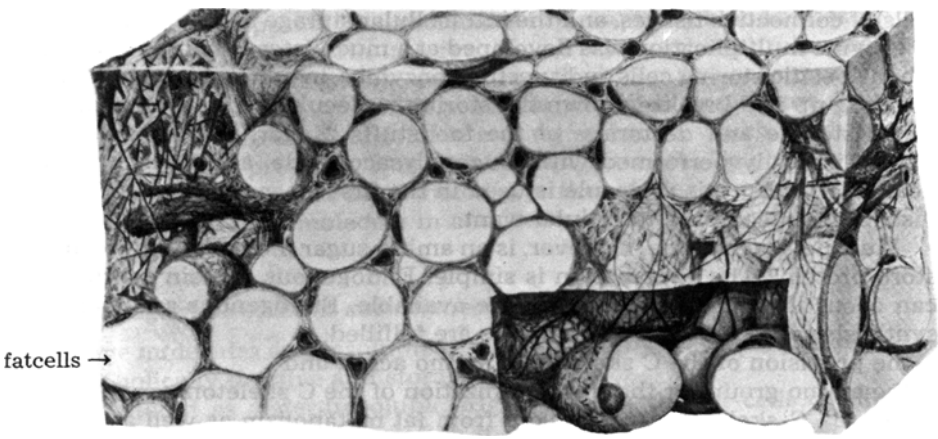



Fig. 2. Fat storage in an overnourished person. A. Maximow (1927)

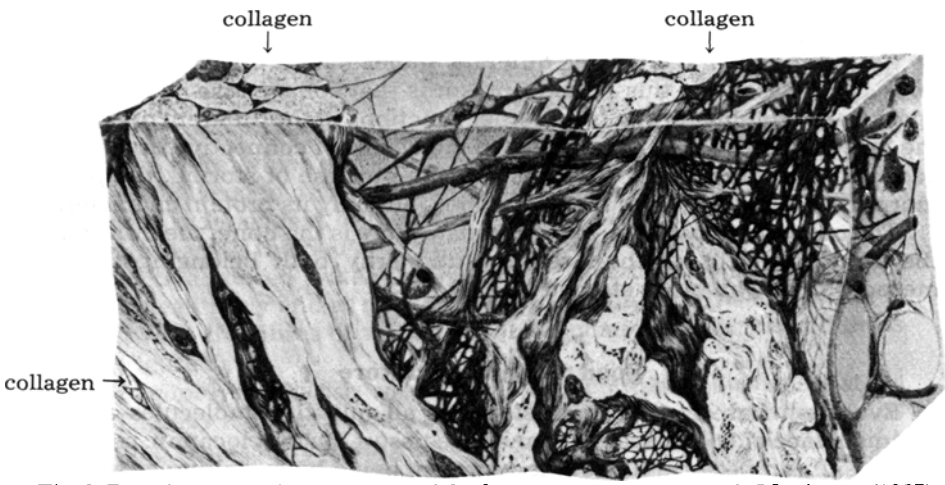



Fig. 3. Protein storage in an overnourished person. A. Maximow (1927)

of the store, each cell of the body is able to pick up any food molecule at any moment out of tissue fluid, and, if want arises, to call off every food molecule from the everywhere-present store without delay by long transportation ways. Even the most genial constructor could not have solved this double-function of food supply and food storage for 60 trillion body cells better than evolution did. If food distribution for only 4 billion living people on this earth would be equivalent to evolution, nobody would suffer hunger or even die of it.

*Subcutaneous tissue* consists of intertwisting collagen and elastic fibers in a ground substance of mucopolysaccharide, the latter changing its state between sol and gel. It takes part in the structure of all organs and is located subcutaneously and between capillary wall and cells.

The streaming conditions of water in connective tissue are similar to those of a well-drained swamp. The diffusion and filtration stream, slowly flowing through the connective tissue, is a solution of fluid food, food for the cells. The flow of the tissue stream is driven by the capillary diffusion and filtration pressures and the massaging pressures of body movements, its composition of food molecules is controlled by the cells, replenished by central regulations, drained by lymph capillaries and venoles.

*The physiological storage of protein according to our doctrine*

The necessity of protein storage arises when in overnutrition the protein-blood level rises. Hyperproteinemia is a dangerous situation in metabolism. It disturbs the rheological qualities of blood by increasing viscosity, retards by hyperoncosis the water filtration from capillaries into tissues. Unlimited increase of hyperproteinemia would quickly lead to death. Endothelial cells stop this dangerous development by taking albumin out of blood, putting it on basement membranes. From here, albumin passes through the pores of basement membranes into tissues. Tissue cells transform albumin into collagen and put it on the collagen fibers of connective tissues which thicken thereby. This protein storage runs parallel to the fat storage in the tissues during the development of obesity. We have seen the results of this physiological storing process of fat and protein in subcutaneous tissues in the Figures 1–3 before.

*But what is the basement membrane?*

Basement membrane, blood, and connective tissues are derived from the mesoderm. They are a genetic and functional unity. The basement membrane is composed of the same material as connective tissue, collagen and mucopolysaccharide, only its knitting is tighter. They both grow thicker and tighter in overnutrition (Fig. 17 c) thinner and looser in hunger (Fig. 17 a). So it is obvious that basement membrane fulfills the same storage functions as the connective tissue itself, being part of it.

*Changes of capillary-basement membrane in hunger*

The diminution of capillary-basement-membrane (BM) thickness in long-lasting hunger has not been investigated in electronic-microscopical research. However, experimental scurvy, which is connected with continuous hunger, has been examined electron-microscopically by several

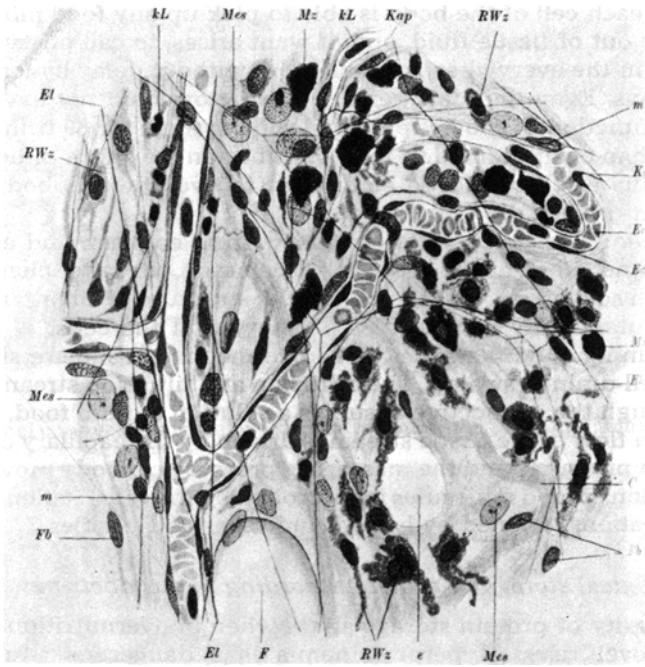



Fig. 4. Tissue of omentum from a normally nourished healthy person. There is collagen (C) and a filled fat cell (F). A. Maximow (1927)

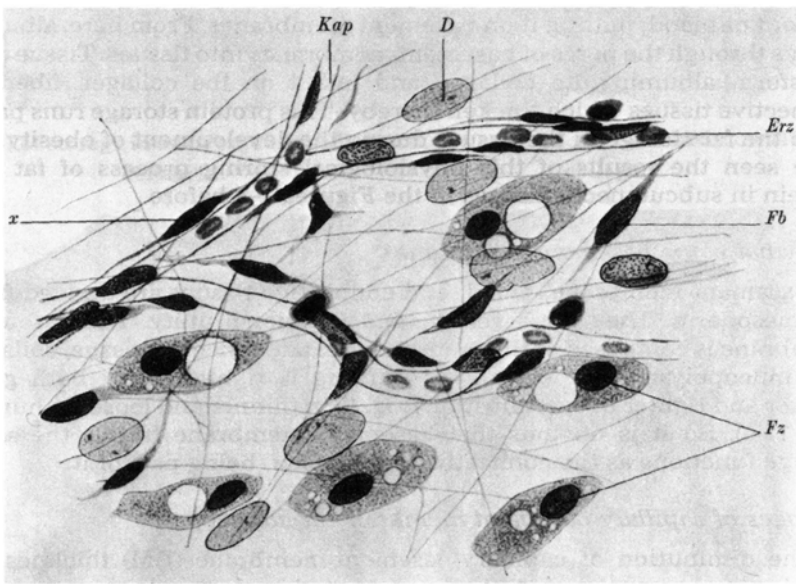



Fig. 5. Tissue of omentum from a rabbit after a long period of hunger. (Fz) Fat cells are empty, collagen has disappeared completely. A. Maximow (1927)

groups of scientists. H. H. R. Friederici et al. (1966) gave about their scurvy-experiments the following report:

"The animals receiving the vitamin C-deficient diet evidenced a decrease in vigor and activity beginning on approximately the 14th day of the experiment. It followed loss of appetite, failure to gain weight, loss of vigor, swelling and tenderness of knee joints. The animals were sacrificed when scurvy was obvious but before the development of severe inanition and/or of marantic state ... The hunger of the animals was quite apparent."

*Authors' comment:*

Due to Friederici's report, one must be aware that of the symptoms, the animals developed some were caused by hunger, others by scurvy.

*Friederici continues:*

"Compared with the controls the capillary BM of scorbutic animals was thinner and appeared excessively tenuous, while there was a concomitant reduction in collagen fibrils. Indistinct delimitations of BM made it unsuitable for precise measurement. BM also seemed to be less effective as a relative barrier in scorbutic animals: When the tracer (ferritin) was seen within intercellular gaps, it tended to pass the BM as well. Pericapillary collagen fibrils seemed to be considerably reduced in their number in those animals." (H. H. R. Friederici et al., Laboratory Investigation, 15, p. 1442–1458; 1966).

Those criteria out of Friederici's scurvy-report are the consequences of protein hunger, in which the animals got into during the experiment. They are the same as result of long-lasting protein hunger in man, in particular: Diminution of collagen-content of BM and intercellular tissues, leading to an attenuation of BM and intercellular tissues. Thereby the diameter of BM becomes smaller, the diameter of BM-pores and the BM-permeability larger. (Friederici's criteria of protein hunger on connective tissues, the diminution of collagen fibers, we have demonstrated already with our Figures 1–5.) So Friederici's results, the BM-diminution in scurvy hunger, fill the last gap in the chain of proof for our doctrine.

*The two storing doctrines*

The presently valid doctrine of nutrition claims that "in overnutrition all surplus calories are stored as fat, and obesity is the only consequence of overnutrition". In our doctrine, however, each food molecule has its own storing molecule in connective tissue. Mind the big difference between the two doctrines and take notice that we have all the proofs for the statements of our doctrine, namely:

All molecules which we call storage molecules have as common characteristics the following qualities:

1. They are unsoluble in water
2. They all multiply in overnourishment and diminish in hunger
3. Their storing place in connective tissue is optimal for all of them.

In spite of those equal qualities and functions, the present doctrine grants the title of a "storing molecule" only to the fat, not to collagen and

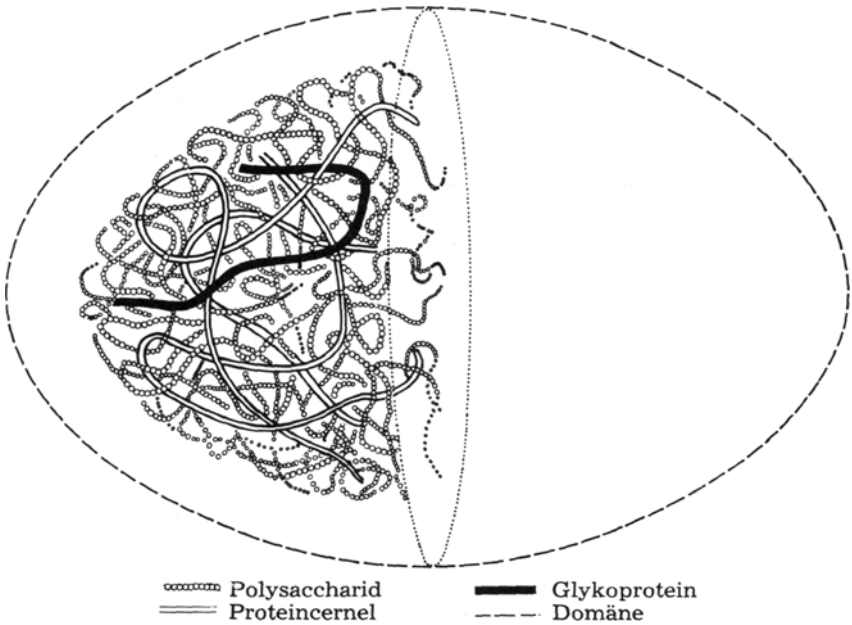



Fig. 6. Mucopolysaccharide molecule. (Luscombe and Phelps, 1967)

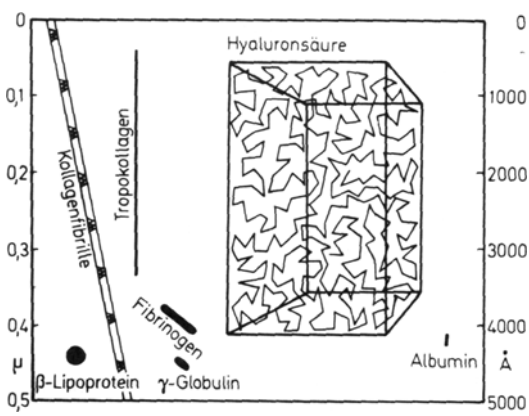



Fig. 6 a. Size-differences of molecules. Hyaluronic acid is a part of the mucopolysaccharid molecule. K. H. Knese (1979).

not to mucopolysaccharide. That is illogical. Of course, all three are storing molecules and many other kinds of molecules, too.

## Pathology of protein transport and storage in man
## According to a speech in the University Umeå, Sweden, April 16, 1980
## Disturbance of protein transport through basement membranes

Basement membrane is the bottleneck of the protein-transport channels from capillary blood to subcutaneous tissues. The diameters of its

pores vary between 28 and 70 Å (F. Hammersen 1974, J. Eigler 1970, B. Hulme 1975).

Molecules with smaller diameters pass the pores without difficulty. All food molecules have considerably smaller diameters, smaller than the smallest diameters of basement-membrane pores, except albumin, which is protein.

With its measurement of 38 against 150 Å (R. G. Galaske et al., 1975), albumin is larger than the smaller pores of basement membranes. The transport of protein through the basement membrane therefore is accompanied by the obstruction of the smaller pores, which represent the majority of basement-membrane pores (F. Hammersen 1974).

*The compensation of congesting hyperproteinemia is the pathogenesis of essential hypertension*

An example of a congested basement membrane shows *Figure 7.* In this experiment (M. G. Farquhar 1964) a rat got an intravenous injection of ferritin. Ferritin is a protein molecule with an iron core (diameter 100 Å). The iron core makes the ferritin visible in the picture. The ferritin enters the wide entrance of pores (diameter 180 Å), but in the narrow middle part of the pore (diameter smaller than 70 Å), ferritin gets trapped.

Each trapped ferritin molecule obstructs one pore of basement membrane. Let us assume that in this picture half of the total diameter of all

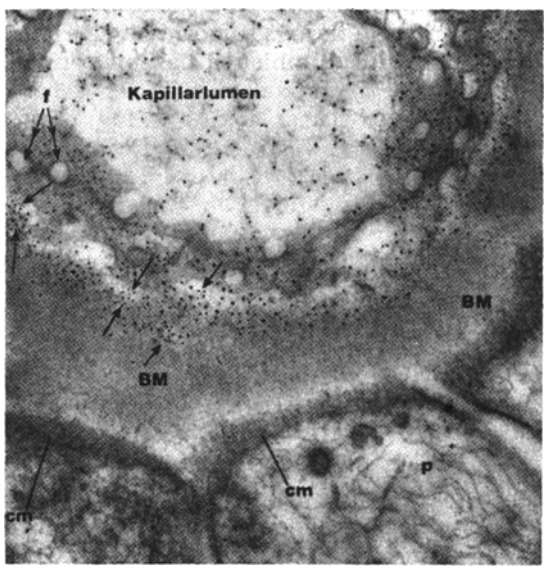



Fig. 7. Capillary of a rat which received a ferritin injection intraveneously 1 hour before death. Ferritin molecules are in the capillary and in the lamina interna of basement membrane. Before the lamina densa the ferritin got trapped. It occludes the pore. (M. G. Farquhar et al. 1964).

BM = capillary basement membrane, f = fenestra of the endothelial cells, cm = epithelial cell membrane.

basement-membrane pores were obstructed. Then only half the physiological capillary water-filtration rate could pass through those membranes. The cells, however, need the whole of the physiological water filtration rate. Regulations therefore must increase the pressure of water filtration. That is attained by elevating the blood pressure accordingly. This experiment demonstrates that basement-membrane obstruction leads to hypertension (G. Simon 1976, C. C. Michel 1974). It is that kind of hypertension which arises from overnutrition. The pathogenic factor in this overnutrition hypertension is the surplus food-protein.

*The regulation scheme and aim of essential hypertension*

The increase of blood pressure, compensating the diminution of basement-membrane permeability for water, produces the symptoms of essential hypertension by the following steps of regulations: If in striated muscles the rate of capillary water filtration declines by diminished basement-membrane permeability, hydrostatic tissue pressure sinks. Lowered hydrostatic tissue pressure, however, is the adequate impulse for smooth muscle cells, which are located at the outside of capillaries, to excrete renin. With tissue fluid, the renin impulse comes through the wall of venoles into the blood and to the regulatory centre of the brain, giving information there about the fall of hydrostatic pressure in muscle tissues. Reacting on this information, the centre emits sympathicotonic impulses, by which the heart-time volume increases. This increase elevates the arterial and capillary blood pressures and raises the water-filtration rate into the underwatered muscle tissues to normality. In this regulation, the arterioles and capillaries with diminished basement-membrane permeability are far dilated so that the maximum effect of increased heart action is directed to the benefit of tissues, lacking water, while all other capillaries of the body with normal basement-membrane permeability have constricted arterioles (J. Brod, 1963) for safeguarding those cells in normal watered tissues against a pathological overwatering. After completion of this regulation, the heart-time volume can return to normal again, as the hypertension from now on is kept high by the spasm of the arterioles in the circulation areas of capillaries with normal permeability. The result of this compensation is the restoration of normal filtration rates in all capillaries, in those with reduced basement-membrane permeability as well as in the others with normal permeability.

## Filter change and glacier transport

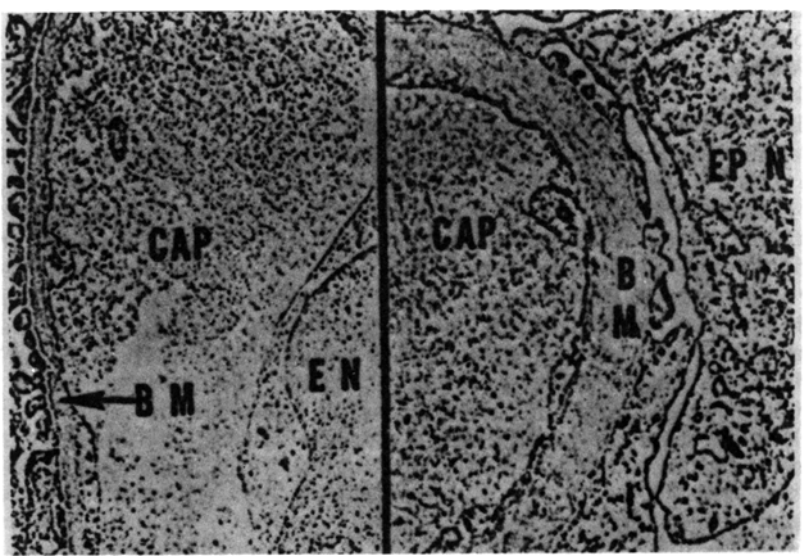
But now the question arises: How can albumin, which is the transport molecule of protein, under physiological conditions permeate basement membranes without obstructing them? The answer is: The filter change takes care of that: In the process of filter change, the endothelial cells take albumin from the blood, transform it into collagen, deposing it as a new layer or filter on the inner side of basement membrane, while at the same time the epithelial cells break off from the outside of the basement membrane the oldest, most obstructed filter. As this process goes on continuously on both sides, filter change goes on continuously as well.

Simultaneously the substance of basement membrane shifts slowly from inside to outside. We call that "glacier stream". Big molecules with diameters larger than pore diameters permeate basement membrane with glacier stream. We call that "glacier transport".

As long as protein transportation is low, pore obstruction and filter change are low as well. If, however, protein transport and pore obstruction increase, filter change accelerates equally. In healthy persons, this physiological filter change keeps the thoroughfare through basement-membrane pores open. But in spite of filter change, there can develop a transport hindrance through basement-membrane pores.

*Basement-membrane thickening is the pathogenesis of adult diabetes*

If in protein overnutrition the onflow of protein molecules on the basement membranes becomes quicker and more concentrated than endothelial-epithelial cells can speed up the filter change, basement membranes obstruct progressively, the outflow of albumin out of blood into the tissues diminishes, the albumin blood level rises. It is the second time that hyperproteinemia occurs in overnutrition, but the present situation of metabolism is different from the former. In the first hyperproteinemia, basement-membrane pores were open, so that superfluous blood albumin could pass into the tissues for storage. In the present hyperproteinemia, the obstructed basement membrane holds back the onflow of albumin, causing hyperproteinemia. Endothelial cells of capillaries stop this dangerous development by taking albumin out of the blood, storing it as collagen on basement membranes. Such protein storage makes the blood




a b

Fig. 8 a. Capillary section of a healthy person.

Fig. 8 b. Capillary section of an adult diabetic. The same magnification. Basement membrane (BM) thickened. By J. M. B. Bloodworth jr. 1964.

thinner, but thickens basement membranes. Thickening up to 1400 Å is physiological (M. D. Siperstein et al., 1973). As, however, protein overnutrition goes on, storage of albumin goes on as well. So basement membranes thicken to 3000 Å and more (M. D. Siperstein et al., 1973). Figure 8 shows the 1000-Å-thick basement membrane of a healthy man and the 3000-Å-thick basement membrane of a diabetic. We today know that all risk-factor patients have thickened basement membranes. But we do not know whether those thickenings have any relevance to the patient or his disease. To solve this problem, we begin with *the driving power for molecule passage through basement membranes.* The transport of food molecules from capillary blood into tissues goes through capillary walls. Their basement membranes oppose against the passage with a resistance, the streaming resistance. Energy is required for overcoming it.

That energy is delivered by the diffusion pressure of permeating molecules. The higher the blood level of a substance, the higher is its diffusion pressure. The blood levels of permeating molecules therefore have to have always that height which produces diffusion pressures by which the streaming resistance of basement membrane is overcome. For the permeation of normal basement membranes of healthy persons, normal diffusion pressures are sufficient, that means: normal blood-sugar level, normal blood-insulin level, normal blood-oxygen tension, normal blood pressure etc. But now the question arises: *How do molecules permeate through thickened basement membranes?* The food molecules permeate basement membranes by diffusion. The diffusion time grows with the second potence of distance, that means (for our question), of basement-membrane thickening. Therefore membrane thickening diminishes membrane permeability. As the basement membrane in this diabetic (Fig. 8 b) is 3 times thicker than in the healthy person (Fig. 8 a), the diffusion time of glucose in this diabetic is 9 times longer than in the healthy person, the cells of the diabetic get only $^1/_9$ of the glucose of a healthy person. The cells of the diabetic, however, need (ceteris paribus) the same amount of glucose as the healthy person. The regulations therefore must increase the diffusion pressure of blood glucose for speeding up the glucose diffusion through the thickened basement membrane. The diffusion pressure of glucose depends on its blood level. The higher the blood level, the higher is diffusion pressure. Regulations elevate therefore the blood-sugar level as long as its diffusion pressure is high enough to push the physiological diffusion rate of glucose through the thickened basement membranes. The regulations fulfill this compensation by producing an adequate hyperglycemia. A hyperglycemia which is not produced by nourishment, but by regulation is called sugar-diabetes. So the thickened basement membranes in patients with adult-diabetes are the cause of that form of diabetes (L. Wendt 1949, M. D. Siperstein 1969).

*The etio-pathogenesis of hypercholesterolemia*

The molecule diameter of LDL- and VLDL-cholestrol molecules is above 150 Å, while the diameter of the basement membrane pores is below 100 Å. Except for the HDL with diameters smaller than 100 Å, all other cholestrol molecules cannot permeate basement membranes (Figure 9).

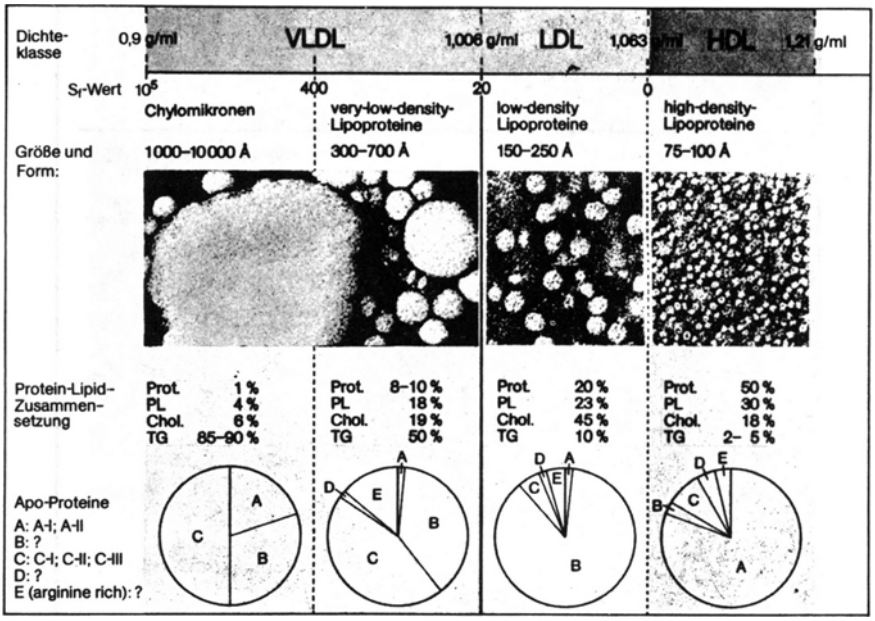



Fig. 9. Characteristics of normal lipoproteins by D. Seidel and G. Schettler, 1977. Sf-Wert = flotation-class in ultra-centrifuge, Prot. = protein, PL = phospholipid, Chol. = cholesterol, TG = triglycerid

Therefore the hindrance of cholestrol permeation cannot be the capillary basement membrane.

Instead, cholesterol hindrance of basement-membrane permeation must be located at a spot of blood circulation where cholesterol permeation under physiological conditions is unhindered. One of the few spots where that is possible is the liver-sinusoid (Fig. 10). That type of capillary wall is missing the basement membrane. Its subendothelial space, the "Dissé-space", contains only a small rest of basement-membrane tissue, very thin reticular fibers with large openings, passable for large molecules like cholesterol (LDL and VLDL). Through this thoroughfare under physiological conditions, regulations can lower an elevated cholesterol blood level after a cholesterol-rich meal by shifting the cholesterol surplus from the blood into the bile ducts. At such occasions, the cholesterol takes its way from the sinusoidal blood through the "fenestrae" of the endothelial cell-layer, through reticular fibers of Dissé-space, through cell membrane and plasma of the liver cell, through the wall of the bile ductules down the bile ducts either for storage into the gallbladder or for excretion into the bowels. All cholesterol food which is resorbed by the bowels goes into the blood and can leave it almost only by this thoroughfare. All cholesterol-level-lowering mechanisms are located in the entero-hepatic cholesterol circulation (downbreak of the cholesterol in the liver cell, cholesterol storage in the gallbladder, cholesterol excretion into the bowels). The cholesterol-blood circulation possesses none of such cholesterol-lowering mechanism except the thoroughfare: Dissé-space to liver cell. As long as

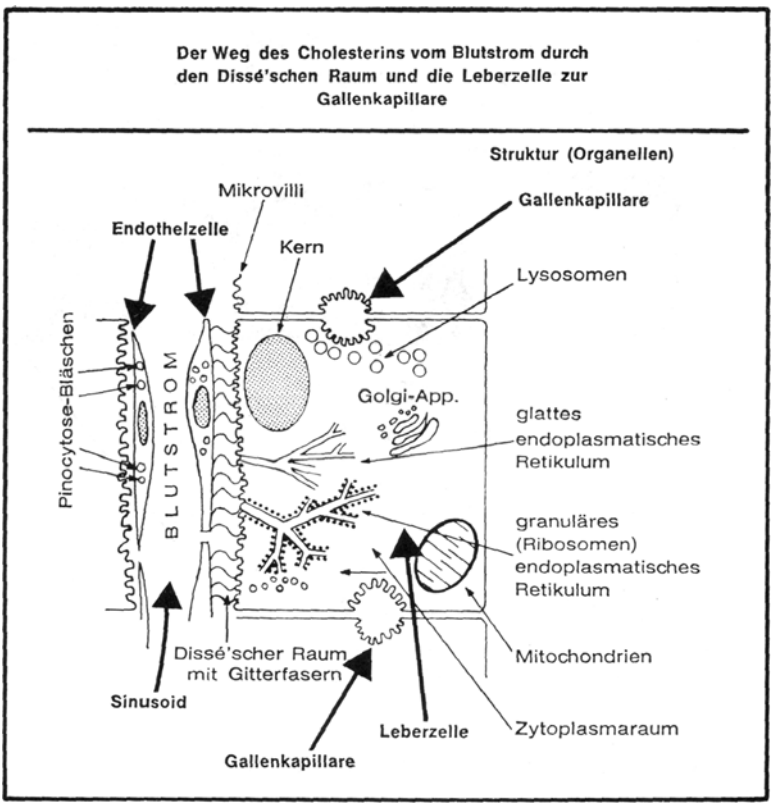



Fig. 10. The way of cholesterol from capillary blood through Dissé space and liver cell into the gall capillary.

this thoroughfare is open, the cholesterol level in the blood is always kept in normal balance, the "essential" hypercholesterolemia cannot develop. But if in overconsumption of protein food endothelial cells of liver sinusoids secrete surplus blood protein on reticular fibres of Dissé-space (Fig. 11), the fibers thicken. This was published by my teacher, R. Rössle, as early as 1907. By this thickening of fibers the thoroughfare narrows, cholesterol congests back into the blood, causing the congestive "essential" hypercholesterolemia. The endothelial cells, not tolerating the congestive hypercholesterolemia, resorb the surplus cholesterol and secrete it subendothelially. As far as endothelial cells of arteries are concerned, cholesterol is secreted on arterial intima; in the long run, that leads to atherosclerosis.

*The third compensation of congestive hyperproteinemia is the pathogenesis of arteriosclerosis*

The continuous storing of protein on capillary basement membranes ends at last with overfilling of capillary membranes, so that capillary endothelial cells have to reduce their storage, while protein overnutrition

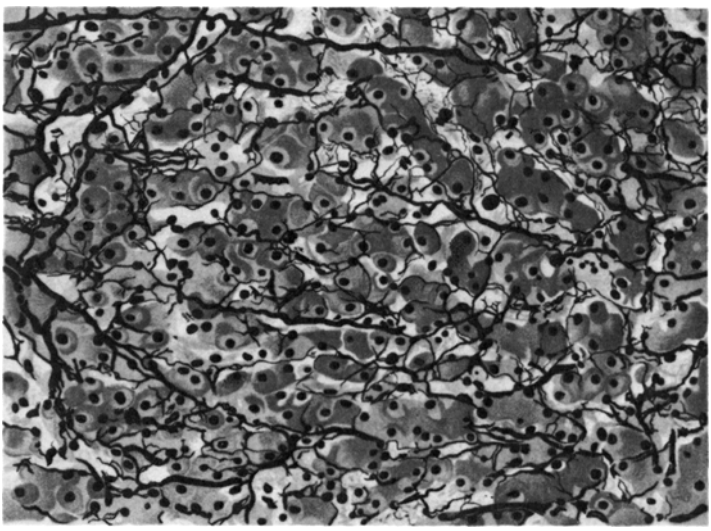


Fig. 11. Protein storage on collagen fibers in Dissé-space of the liver: The dark lines between liver cells are thickened fibers in Dissé-space (subendothelial space).
Robert Rössle (1908)

goes on. So protein congestion into the blood increases, elevating the protein blood level again. "The majority of arteriosclerosis forms are related to a disturbance of the seeping of blood plasma" (W. Doerr 1978). It is the third time that hyperproteinemia occurs in overnutrition, but again the situation is different: In the first time of hyperproteinemia the surplus of blood protein flew through open pores of basement membranes into the tissues for storage, in the second time the obstructed basement membrane made it necessary, that the surplus of blood protein was stored on capillary-basement membranes.

In the present situation capillary endothelial cells cannot compensate this oncoming danger ony more, as basement membranes are overfilled. But evolution has developed a compensation even for this dangerous development by:

*Protein excretion*

Not all protein-overnourished people develop microangiopathy and risk factors. There is a certain percentage of man, about 25 %, who can bear protein overnourishment the whole life without overfilling their protein stores, staying healthy, except for obesity. How is that possible? The molecule by which the body excretes surplus protein, is urea, to a very small extent also uric acid and ammonium. If the body has to excrete protein, it suffices the excretion of the amino group $NH_2$, as a desaminated amino acid is a fatty acid which can be metabolized or stored in fat cells. Urea is excreted by the kidneys.

As only the liver cells possess the urea cycle, they only are able to protect the body in times of protein overnourishment against an overfilling of protein stores by increased urea production.

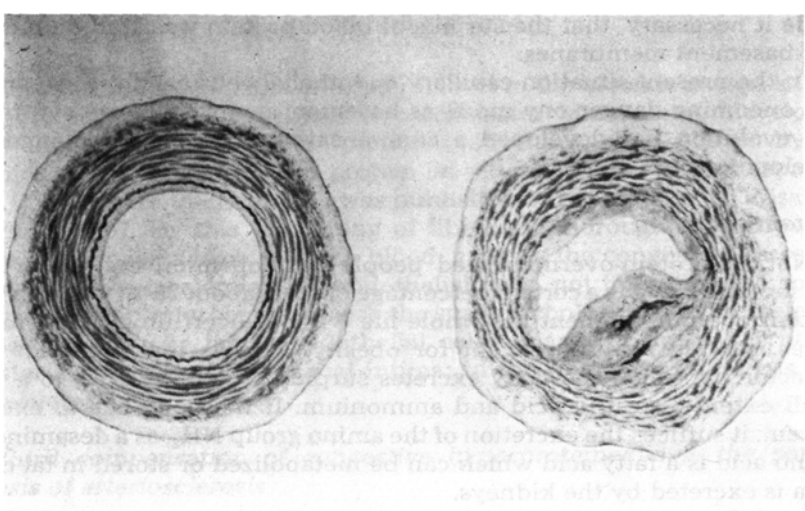
Urea, $CO(NH_2)_2$, is the ideal molecule for protein excretion. With that small molecule the equivalent of two amino acids are excreted. People with a high maximum of urea cycle functioning stay healthy even in protein-overnourishment. On the other hand: *A low maximum of urea cycle functioning is the heredity-factor of arteriosclerosis etiology.*

**Pathogenesis of arteriosclerosis**

The capacity of the basement-membrane protein store is limited. Limited as well is the ability of protein excretion by the uppermost activity of urea-cycle enzymes. If basement membranes are overfilled with protein, while the protein intake by food is higher than the ability of urea cycle for protein excretion, the blood of that person comes under increasing pressure for protein storage. This pressure surpasses at last the threshold of arterial endothelial cells, which under physiological conditions do not store protein. Now they begin with protein storage on arteries, mixing the stored protein with the surplus blood cholesterol and all other congested blood-molecules, which are stored there as well. That is the pathogenesis of arteriosclerosis (Fig. 12 and Table 2).

*Table 2* demonstrates the pathological protein storage on blood-vessel walls and the pathogenesis of heart infarction in the course of an uninterrupted overnutrition with animal protein. There is no hypothesis in this reaction chain. No link is missing, every link is a fact. It begins with the etiological factors of arteriosclerosis, it terminates with the heart infarction. The heredity factor being the functional weakness of urea cycle, the environment factor the protein overnutrition.

If one of the two etiological factors is missing, the person stays healthy. If both etiological factors come together in one person, hyperproteinemia is inevitable. In spite of so many compensations, fighting against hyper-



a b

Fig. 12. a = healthy artery, b = arteriosclerosis.

proteinemia, heart infarction or stroke will occur, if not in due time a hunger or a protein-fasting period interrupts the continuous overburdening of the body with protein, forcing regulations to take the daily protein

Table 2. Etiopathogenesis of alimentary angiopathies.

*Pathological protein storage*

*Etiology*

*Heredity factor:*
weakness of protein break-down enzymes of endothelcells or (and) weakness of enzymes of urea cycle

*Environment factor:*
protein overnutrition

*Pathogenesis*
Hyperproteinemia
*hemoconcentration*

↓

capillary endothelial cells resorb blood protein, transform it into collagen and store it on basement membranes

↓

*Pathogenesis of microangiopathy*

thickening, obstruction and diminution of basement-membrane permeability (hypopory), blood-level elevations by congestion, risk factors.

↓

diminution of capillary filtration and diffusion rates, damming of molecules, hindered in membrane-permeation, cells lacking them.

↓

*Microangiopathy*

↓

compensatory blood-level elevation of all dammed molecules until their filtration and diffusion power is able to overcome the increased streaming resistance of the thickened membrane.

↓

*Effect of risk factors (hypoporopathies)*

↓

capillary filtration and diffusion rates and tissue levels of food molecules are lifted to normal again, the lack of cells is removed. That is the compensatory aim of risk factors.

↓

*Continuous storing overfills capillary basement membranes,* blood congestion increases, blood levels of risk factors elevate more, overstepping the threshold of arterial endothelial cells, which now begin with storing of risk-factor molecules.

Protein — Cholesterol — Urci acid — Insulin — Growth hormone — Glucose *and others*

Deposition of congested blood molecules on intimae of arteries

*Arteriosclerosis, arteriogenic infarction, coronarogenic heart infarction*

Deposition of congested blood molecules on capillary basement membranes goes on, until

*insufficiency of basement-membrane-function: capillarogenic tissue degeneration, capillarogenic heart infarction*

requirement of the body off the stores, which empty thereby, restoring the health of the patient. This reaction chain can be understood as the fight of regulations against hyperproteinemia in protein overnutrition.

So risk factors, basement-membrane thickening, and arteriosclerosis are neither fat nor carbohydrate metabolic diseases, as present doctrine claims, but protein-storage diseases, and the pathogenic factor in overnutrition is neither fat, nor carbohydrate, but protein.

*The pathogenesis of primary multifactorial angiopathies*

So far we delt in our considerations only with one factor of blood pollution, the hyperproteinemia. However, with the air we inhale, the food we eat, the water we drink, polluting substances enter our blood. Each citizen of a big city has continuously a multitude of polluting substances in his blood, for instance: Carbon monoxide, lead, cadmium, dust of different materials, antibiotics, medicaments, nitrosamine, not-self proteins, heteroproteins, carcinogens, and many others. Blood-vessel walls and immunity system are continuously at work, cleaning our blood and our tissues from all of them, preserving our health, unnoticed by us.

*About blood-polluting proteins*

Protein of streptococcus, which penetrated into the blood, is "not-self" protein. The immunity system produces antibodies against streptococcus antigen, whereas endothelial cells resorb streptococcus antigen and antigen-antibody complexes, breaking them down (Diaz et al., 1973) or, if there are too many of them, deposing the rest unbroken on basement membranes (Conn 1976, F. Weidner 1975, 1979).

The same happens with insulin, which the diabetic injects himself. The therapeutical insulin comes from cattle and pig. It is "not-self" protein. The immunity system reacts alike with the production of antibodies, and endothelial cells break down "not-self" insulin or depose it on basement membranes.

Another kind of blood-polluting protein is heteroprotein. An example is the carbon monoxide hemoglobin. A cigaret-smoker, who inhales the smoke, gets carbon monoxide into his lungs and into his capillary blood. The reaction of carbon monoxide with hemoglobin is 300 times quicker and stronger than the hemoglobin reaction with oxygen. In consequence, the total of carbon monoxide binds quicker and tighter with hemoglobin. Such hemoglobin cannot transport oxygen anymore. The hemoglobin molecule, bound to carbonmonoxide, has become a dead molecule. Erythrocytes, filled with carbonmonoxide-hemoglobin, are dead cells. They hemolyze, the carbon monoxide-hemoglobin flows into the blood and produces a heteroproteinemia. The endothelial cells take those dead molecules out of blood, break them down, and the rest, which is too much for them, they deposit unbroken on basement membranes. Endothelial cells perform the clearing of blood from all those pollutions simultaneously in the same way, as we have explained in Table 2 (L. Wendt, 1972).

The partisans of the present doctrine were until recently of opinion that the arteriosclerogenic factor of smoking would be the nicotin. Only in the last years, publications multiply in which carbonmonoxide is suspected as

Table 3. Course of multiple blood pollutions in different persons.

The clearing of several blood pollutions in a healthy person with strong lysosomal break-down enzymes of endothelial cells.

| surplus protein of over-nutrition produces | carbon-monoxide hemo-globin in blood of cigaret-smoker produces | invasion of bacteria into the blood in streptococ-cus pharyngitis produces |
|---|---|---|
| ↓ | ↓ | ↓ |
| hyperproteinemia by euproteins | heteroproteinemia | antigenemia |
| ↓ | ↓ | ↓ |

Lysosomal strong endothelial cells resorb the disturbing proteins, breaking them down to amino acids, which they rebuild to body protein. So blood pollution is cleared without any harm to the person.

Table 4. Clearing of the same blood pollutions in a person with weak lysosomal break-down enzymes of endothelial cells.

hyperproteinemia — heteroproteinemia — antigenemia

↓

Endothelial cells break down disturbing proteins, secreting the undigested rest on basement membranes.

meaning: physiological protein-storage up to 1400 Å basement-membrane thickness. Above 2000 Å meaning:

| microangiopathy by euprotein: benign capillarose | microangiopathy by heteroprotein: capillaritis | microangiopathy by antigen: malign capillaritis |
|---|---|---|
| *making* | *making* | *making* |
| benign risk factors: adult diabetes, unconplicated hypertension, gout | severe risk factors, diabetes and hypertension, complicated by stroke and heart infarction | diabetogenic glomerulos-cleritis Kimmelstiel-Wilson, malign hypertension, malign retinopathy with blindness, stroke, heart infarction |
| ↓ | ↓ | ↓ |
| *life expectancy* 60–75 years | *life expectancy* 45–55 years | *life expectancy* 25–40 years |

Table 5. If capillary basement membranes are overfilled, disturbing blood proteins are deposited on intima of arteries.

Thereby is

↓

| hyperproteinemia leading to arteriosclerosis | heteroproteinemia leading to arteriitis | antigenemia leading to malign arteriitis |
|---|---|---|

Table 6. From microangiopathy, however, the further development of the disease can take its direction into tissues. In this course, disturbing proteins, deposited on the inner side of basement membranes, are transported by glacier-transport through basement membrane. Arrived at the outside of basement membrane, proteins are broken down by epithelial cells to amino acids. If there are too many disturbing proteins, epithelial cells let the undigested rest pass into tissues.

| Arrived in tissues | | |
|---|---|---|
| euprotein produces fibrosis, for instance benign liver fibrosis | *heteroprotein* produces scirrhosis, for instance liver scirrhosis | *antigen* produces autoimmun diseases (antigenopathies), for instance lupoid hepatitis. |

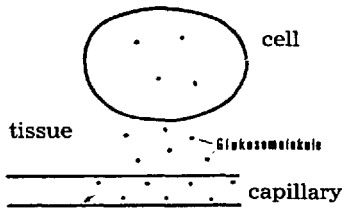
the real arteriosclerogenic factor of smoke. F. H. Epstein (et al. 1979) emphasizes that. In Epstein's pathogenesis, however, the carbon monoxide is supposed to damage endothelial cells of arteries, whereby the development of arteriosclerosis is favoured. In our doctrine, however, is the resorption of blood pollutions, their breaking down and storage on blood-vessel walls the physiological function of endothelial cells.

In Table 1 it was the overnourishment by animal protein which led to hyperproteinemia and capillary basement-membrane thickening by euprotein. In such cases we speak of monofactorial angiopathy. But in most cases several pollutions come together, leading to *the development of multifactorial angiopathy.* As an example we assume that a patient 1. eats too much animal protein, whereby he has a hyperproteinemia; that he has 2. carbon-monoxide hemoglobin in his blood, being a heavy smoker; and 3. that he has, after a streptococcus pharyngitis, streptococcal antigen in his blood. He then has three disturbing proteins in his blood: 1. hypereuproteinemia, 2. carbon monoxide-hemoglobin heteroproteinemia, and 3. strepto-antigenemia. The blood-clearing mechanisms go into action against all those blood pollutions simultaneously. The Tables 3–6 demonstrate the different courses blood pollution can take in different patients.

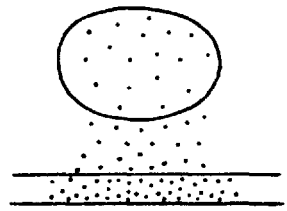
### The difference between juvenile and adult diabetes

The adult diabetes develops together with other risk factors in persons overnourished with animal protein by thickening of capillary basement membranes. The juvenile diabetes is a totally different disease. It has nothing to do with nutrition. It begins with healthy capillaries and normal body weight, when children with hereditary weakness of the immunity system get as complication of a virus infection a pancreatitis. Thereby the function of the islet cells, the production of insulin, gets lost. For explaining its pathogenesis, we begin with the sugar metabolism of a healthy person.

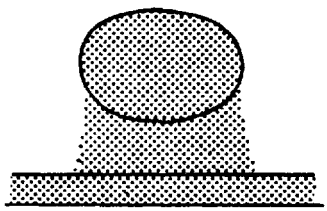
The Figure 13a represents "capillary, tissue, and muscle cell" of a healthy person at rest, Figure 13b at work. The points in the figure stand for glucose molecules. Glucose multiplies at work for the production of increased contraction energy of the muscle cell. For this purpose, intracellular insulin transforms glucose into glycogen. From glycogen muscle cells gain their contraction energy.



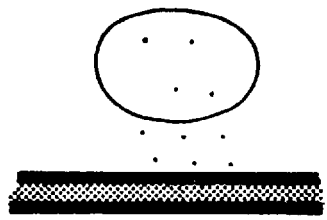

a Healthy person at rest.



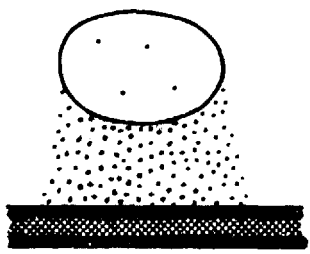
b Healthy person at work.



c Juvenile diabetic.



d Adult diabetic: thickened basement membrane.



e Adult diabetic: thickened basement membrane and narrowed, elongated interstitial tissue.

Fig. 13.

The healthy person takes the additional glucose for performing body work from the store, the liver. In a healthy person, transportation ways through capillary wall and tissues are free and open. In consequence, the characteristics of the glucose levels in a healthy person at work are:

1. Additional blood glucose for the production of increased contraction energy comes from the store, the liver (and not from congestion).
2. The increased glucose transport from the store to muscle cells increases the glucose level equally along the whole transport way, in the blood, in the tissues, and in the cells.
3. Glucose transport is accelerated along the whole transportation way due to elevated glucose-diffusion pressures and accelerated blood circulation.

Those are the *characteristics of blood-level elevation of activity in a healthy person.*

Figure 13c shows the glucose levels in the 3 compartments of a juvenile diabetes. Again the glucose level in the 3 compartments are equally elevated on account of open transportation ways. Again the additional

glucose comes from the store, but in juvenile diabetes glucose levels are considerably and equally elevated in all 3 compartments. The cause is the lack of insulin. With insulin, the muscle-cell builds up its energy molecule "glycogen". Without insulin, the muscle slides into dynamic insufficiency. To prevent this danger, regulations increase the glucose level in the cell. High cell glucose acts similarly glycogeneticly as insulin. As the additional glucose for this compensation comes from the store (the liver), the glucose levels on the whole transportation ways from the store to the muscle are elevated equally. Those are again the *characteristics of a compensatory hyperglycemia, which is a level elevation of activity.*

The Figure 13d demonstrates the glucose levels of an adult diabetic. The basement membranes of capillaries are thickened, representing a transport hindrance. The glucose level in front of the hindrance is increased by congestion, behind the hindrance diminished, causing cellular malnutrition.

In Figure 13e not only the basement membrane is thickened, but also the transportation way through the tissue is elongated and narrowed. That is a second hindrance. In front of both hindrances glucose congests back. That causes a congestive hyperglucosis in the blood and in the tissue. In congestive blood-level elevation 1. the blood-level elevation comes primarily from congestion, 2. the transportation speed is retarded along the whole transportation way, upstream by congestion, downstream by lowered diffusion pressure, and 3. the glucose level upstream of the hindrance is elevated, downstream it is lowered. Those are *the characteristics of congestive hyperglycemia* of the adult diabetic. Those differences between elevated blood levels of activity and of congestion are the difference between the juvenile and the adult diabetes. They are valid for all congested molecules, for albumin, fat, lipoproteins, uric acid, oxygen, and others. The level elevations of activity and compensation are physiological and never pathogenic. The congestive level elevations, called risc-factors, are always pathogenic, leading to micro- and macroangiopathy. The elevated blood parameters of risk factors are all congestive elevations. In the recent-onset juvenile diabetes hyperglycemia and, if present, hyperlipemia are bloodlevel elevations of activity, because in the beginning of this disease the juvenile diabetic has healthy capillaries and arteries.

*The microangiopathy in juvenile diabetes*

The deadly complication of juvenile diabetes is the acidotic coma, not the angiopathy. The coma is prevented by insulin therapy. The micro- and macroangiopathy of juvenile diabetes does not come from diabetes, but from the insulin therapy. The therapeutical insulin is immunologically "not-self protein" as it comes from pig and cattle. "Not-self protein" induces the immunity system to produce antibodies. Endothelial cells are the guardians of the cleanness of blood. "Not-self protein" in the blood means blood pollution. Endothelial cells take the "not-self insulin" out of blood and break it down to amino acids. If it is too much, they secrete the rest unchanged on basement-membranes. That leads in the run of 2–6 years to thickening and inflammation of capillaries, to the malign form of microangiopathy.

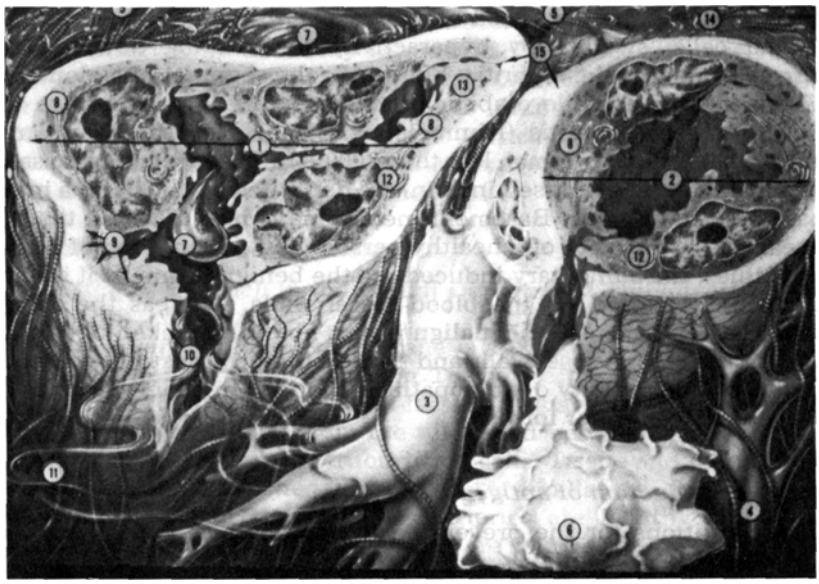


Fig. 14. 1. Venole, 2. capillary, 3. activated epithelial cell, 4. fibroblast, 5. fibroblast processes, 6. lymphocyte, 7. granulocyte, 8. endoplasmatic reticulum, 9. mitochondrias, 10. fissure, 11. blood-plasma exudate, 12. Golgi apparatus, 13. tonofilament bundle, 14. collagen fibers, 15. capillary basement membrane.

H. G. Fassbender (1976)

Only from now on, juvenile diabetes is a risk factor with congestive blood-level elevations, which lead to the malign form of micro- and macroangiopathy. As the arteriosclerogenic factor in juvenile diabetes is an antigen, its deposition on the capillaries and on the intima of arteries causes the malign capillaritis and endarteriitis.

Figures 14, 15, and 17c show different stages of antigen-induced capillaritis, Figure 14 the acute capillaritis of a patient with acute rheumatoid

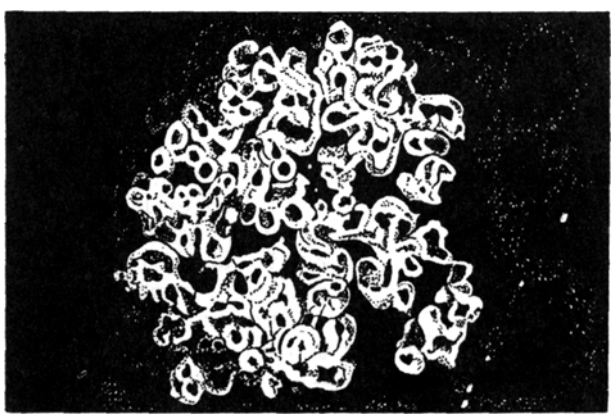


Fig. 15. Antigen-antibody-complex depositions, fluorescent, on glomerulus capillaries in allergic nephritis. By E. R. Unanue and F. J. Dixon

arthritis. You see the thickened basement membranes and the endo- and epithelial cells, swollen by hyperactivity in breaking down antigen. Figure 15 is an allergic nephritis, Figure 17c the segment of a glomerulus capillary from a juvenile diabetic who died with 35 years of age from diabetic glomeruloscleritis (Kimmelstiel-Wilson). Here basement membrane is 5000 Å thick (normal, less than 3000 Å) and additionally masses of collagen and antigen (not-self insulin) are deposited on the lamina interna of basement membrane. Basement membrane is here 20,000 Å thick. Its permeability is only 2 % of a healthy person. The patient died of it. In all angiopathies, the alimentary induced are the benign forms, as it is euprotein, which is stored on the blood-vessel walls, whereas the antigen-induced angiopathies are the malign forms, not only thickening, but also inflaming the blood-vessel walls and tissues, thereby mostly leading to an early death. The severity of angiopathies, induced by heteroproteins, lies between the two former forms.

*About the production of antigen-free insulin*

The conditions for the prevention of angiopathies in insulin-treated diabetes are the following:

1. The production of genuine human insulin
   That aim has been achieved (by Hoechst and Ciba-Geigy), but the production is too expensive, and the amounts produced are too small for general therapy.
2. To reach the highest possible degree of cleanness in the production of insulin out of animal pancreas
   Also this aim is reached by the production of mono-component insulin, which irritates the immunity system less, but still too much for being indifferent.
3. A third way was found by K. Valdenaire and W. Klein (1979). They broke off from the insulin-molecule the N-terminal aminoacid phenylalanin (Phe). The immunogeneity of this "Des-Phe-Insulin" is 51 % reduced.
4. The gentechnological production of insulin by bacterial cultures has attained lately such efficiency that in the near future genuine human insulin will be offered enough for everybody.

*The main differences between the two diabetes doctrines*

In the present valid doctrine, only blood-level elevations are considered. The thickened capillary basement membrane and its congesting effect on the glucose blood level in adult diabetes is not taken notice of. In consequence, the difference between the two kinds of diabetes could not be acknowledged and is still unknown in valid doctrine up to the present day. Eppinger, Vienna, wrote: "Almost every important invention begins with a model experiment." Figure 13 is our model experiment, a simple drawing, by which we acknowledged the characteristics of the glucose levels in the three compartments (blood, tissue, and muscle-cell) of the healthy person, the adult diabetic and the juvenile diabetic. I proved the conclusion which I derived out of this model experiment (by experiment) and published it the first time in 1948 (Arch. inn. Med., Vol. 1, part 3,

page 1. 1949), repeating it several times since. But the partisans of present doctrine do not take notice of my arguments. They satisfy themselves with the remark that etiology and pathogenesis of thickened basement membrane and its significance in diabetes is unknown, and they go on in considering the blood-level elevation as sufficient for understanding the diabetes in research and treatment, whereas the parameter, which matters most in diabetes, is the tissue-glucose level.

*The capillarogenic tissue degenerations*

According to a speech in the Dental Department, University of Umeå, Sweden, April 15th, 1980.

The thickened basement membrane is a transport hindrance in both directions, upstream and downstream. The congestions upstream of thickened basement membranes, the risk-factors, we have delt with before. The consequences downstream from the thickened basement membrane are lowered tissue levels and undernourished cells. Tissue and cell malnutrition on account of diminished permeability of capillary wall can be proven only by the fact that the supplying arteries are healthy and free of arteriosclerosis, while the capillary walls are thickened. For being able of delivering this proof, one needs an electronic microscope. As we do not possess such an instrument, we let us report the capillarogenic cell malnutrition by G. Brehm (1977). Brehm reports in Springer's handbook of internal medicine 1977 about tissue gangrene of foot by microangiopathy without arteriosclerosis (Figure 16):

"The arteries leading to the undernourished region have normal pulses. In the capillarogenic undernourished region the skin discolours to cyanotic-red, at some spots with blisters. When necrosis develops, the discoloration changes into a blackish-red. The gangrene can develop dry or moist, leading to a quick destruction of tissues. Bacterial superinfection, lymph-

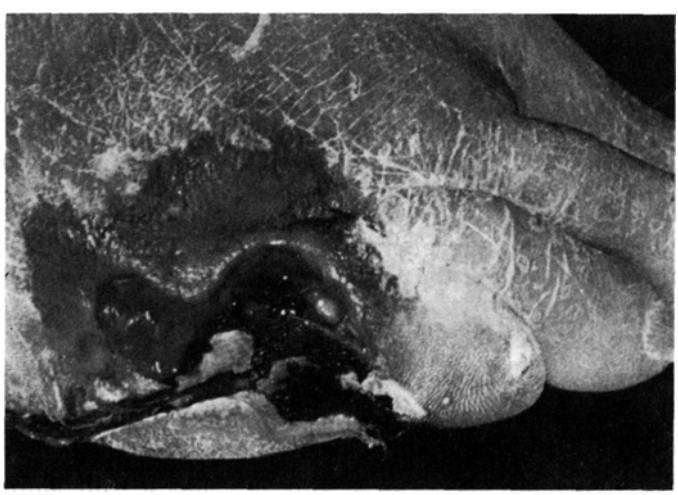


Fig. 16. Capillarogenic necrosis of foot. The arteries are free of sclerosis and stenosis. The capillary basement membranes are thickened. G. Brehm (1977)

angitis, fever, toxic reactions of the blood follow. In the electron microscopical picture, the capillaries in the gangrenous region have thickened basement membranes due to collagen excretions. Degenerations due to microangiopathy can occur in every tissue of the body, in kidneys as diabetic glomeruloscleritis Kimmelstiel-Wilson (Fig. 17c), in the eyes as diabetic retinopathy with characteristic thickening of small arterioles, capillaries, and venoles. Also parodontosis is in most cases a capillarogenic degeneration, the benign form caused in overnourished persons by deposition of surplus food protein on basement membranes, the malign form in juvenile diabetes by the deposition of not-self-insulin (antigen). Handelsmann et al. (1962) found in 79 % of diabetics thickened basement membranes of skin capillaries by collagen deposits. These results have been confirmed by many other investigators."

So far the report by G. Brehm.

A frequent tissue degeneration is the heart infarction. The first definition of heart infarction gave Ziegler in 1887. His definition was: "A necrosis, produced by the coronary artery occlusion, usually by an occlusive thrombosis." However, some heart infarctions have no coronary occlusion (G. Baroldi et al., 1979), but a microangiopathy (S. M. Factor et al., New Engl. J. Med. 302, 384, 1980). In such cases the diminished permeability of a thickened capillary basement membrane is the cause of cellular malnutrition and necrosis. We therefore distinguish between arteriogenic and capillarogenic infarctions. Parodontosis is mostly a capillarogenic infarction (Frantzis et al., 1971).

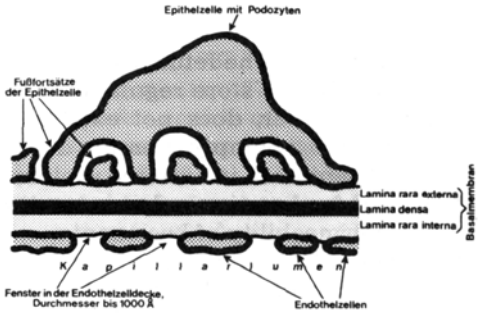
**We summarize**

All degenerations mentioned in this speech have their cause to a small percentage in blood pollution by "not-self-protein", the majority in the overnourishment with animal protein. It leads to overweight and risk factors. Overweight is valid for 50 % of the German population. Risk factors are caused by thickened, minor permeable capillary-basement membranes. Such capillaries can produce tissue degeneration and necrosis at any spot of the body any time. So capillarogenic tissue degeneration and infarction might be one of the most frequent diseases in overnourished persons. That so far seldom considered diagnosis might be one of the most frequent diseases in the western nations in our time. This disease therefore should be taken into the differential diagnosis of every ailment with unknown origin in overnourished adult persons. The most frequent capillarogenic degenerations are the heart and the cerebral infarction, the gangrene of the foot, the diabetic glomeruloscleritis (Kimmelstiel-Wilson), the retinopathy and the parodontosis.

**The three filling stages of basement-membrane (BM) store in electronmicroscopical picture**

*The empty BM store in long-lasting hunger*

BM of the ripe human fetus (Figure 17a) has a thin lamina densa, comprising only ¼ of its total thickness, the laminae rarae on both sides are almost empty spaces, comprising ¾ of its thickness.




Schematische Darstellung der normalen Kapillarwand nach K. H. Bichler, 1975.


Fig. 17 a. The empty BM store after long-lasting hunger.


Fig. 17 b. The partially filled BM store of a healthy person.


Fig. 17 c. The overfilled BM store of a risk-factor patient.

*Explanation:* The fetus uses all available protein for building up body substance. In the store regulations depose only surplus protein. Surplus protein, however, does not exist in fetus. Therefore his BM-store, the laminae rarae, is empty. Lamina densa, however, is not store, but filter. It stays existent even in extreme protein hunger of long duration. The empty store is fit for function only in one direction, for accepting protein.

The permeability of basement membrane with empty stores is high, as thickness of BM is small and its pores are relatively large, concluded from the light gray, in which lamina densa appears in the electronmicroscopical picture (17a). Light gray of BM means loose knitting of its collagen fibres, means large distances between them.

Basement membrane of an adult person after protein hunger of long standing (we have not found so far that electronmicroscopical picture in literature) will appear pretty close to that of the fetus in Figure 17a.

*The partially filled BM store of a healthy person*

*Figure 17b:* Glomerulus capillary of a normally nourished rat.
BM = basement membrane
EN = endothelial cell
EP = epithelial cell
P = podocythe

Thickness of glomerulus BM in rat is 1000–1500 Å, in man up to 3000 Å. In the adult healthy individual, lamina densa comprises $^1/_3$, the laminae rarae together $^2/_3$ of BM thickness. The gray of laminae rarae is in the healthy always lighter than that of lamina densa. It means that the knitting of collagen fibers is looser, the calibre of pores larger than in lamina densa. The BM store with that appearance has storing capacity still vacant, is fit for functioning in both directions, to give and to take protein. The permeability of BM in Figure 17b is that of a healthy individual.

*The overfilled BM store of risk-factor patient*

*Figure 17c* is a section of a glomerulus capillary wall from a juvenile diabetic who died after 19 years of insulin treatment of diabetic glomerulosclerosis (Kimmelstiel-Wilson). BM in that patient has changed in three points:

1. The total diameter of BM is thickened to 5000 Å instead of maximal 3000 Å.
2. BM has on its whole diameter the same dark gray pattern as the lamina densa. The laminae rarae do not contrast against lamina densa by a lighter gray which is caused by partial inner occlusion of BM.
3. Masses of storage protein are deposited subendothelially on the inner side of basement membrane (D), narrowing, sometimes even occluding, the capillary lumen.

ad 1. The thickened basement membrane in one or the other or all capillary bloodstream regions has been acknowledged as the reliable, never missing symptom of risk-factor diseases (hypoporopathies). Thickened reticular fibers in Dissé space of liver cells were found by my teacher, Robert Rössle, 1907 and 1908 in obesity-diabetics, 1923

by L. Aschoff also in other capillary regions, 1963 by M. D. Siperstein et al. in thorough quantitative measurements, 1973 we proved the thickened reticular fibers in Dissé space as cause of essential hypercholesterolemia, in 1977 U. Fuchs found the thickened BM in patients with essential hypertension, 1974 E. B. Feldmann et al. in patients with gout, 1978 J. Gärtner et al. in heavy smokers, 1963 M. D. Siperstein in obese hyperinsulinemia patients. As cause of BM thickening we suspected in our hypothesis of 1948 a disturbance of blood-euproteinemia by hyperproteinemia or by heteroproteinemia or antigenemia.

ad 2. The partial inner occlusion of BM is the forerunning symptom of BM thickening and most probably as reliable as the thickening in risk-factor patients.

ad 3. In Figure 17c, the protein store of BM (the laminae rarae) is completely filled by thickening and by inner occlusion of BM; in fact the store is overfilled already, its storage capacity is exhausted. The inflow of albumin into the blood, however, goes on, as overnutrition of the patient goes on. Unlimited hyperproteinemia would mean sudden death by hyperoncosity and hyperviscosity. To prevent it, endothelial cells change the chemically and metabolically active albumin into the inactive collagen and excrete it subendothelially. The overfilled BM is unable to take it into its store. So the collagen stays in subendothelial space, accumulating there in irregular deposits, occluding the capillary lumen and diminishing BM permeability more and more.

So the above-mentioned three symptoms are the characteristics of the overfilled BM store. The function of that BM store is reduced to spending protein only.

Permeability of that BM with its deposits is extremely lowered, approximately to 2 % of a healthy person. The cells behind that capillary wall died in necrosis, the diabetic patient died of that microangiopathy, the diabetogenic glomeruloscleritis Kimmelstiel-Wilson.

## The silent change of opinion

On the symposium "Science and Practice of Nutrition" (Gottlieben, Switzerland, May 2, 1980), P. Schmidsberger explained the difference between the present valid doctrine of nutrition and the "Wendt doctrine", as above formulated. In the succeeding discussion, D. Hötzel, Professor at the University of Bonn, Director of the Institute for Science of Nutrition, contradicted the above-mentioned formulations arguing that the two doctrines were not as controversial as we thought.

According to Hötzel, man can store protein. On my additional question, whether his statement is restricted to intracellular protein storage only or whether it includes the augmentation of collagen in tissues and on capillary basement membranes as a protein-storage process and the collagen as a storage-molecule, too, Hötzel answered that the protein storage in collagen is not only his opinion, but is also accepted in recent years by the majority of nutrition scientists. However, some of them still may adhere to the old doctrine of the unstorability of proteins.

The thickened basement membrane of overnourished risk-factor patients is according to present doctrine unknown in etiology and pathogenesis. In our doctrine, basement membrane is in times of danger, when the tissue store cannot prevent a growing hyperproteinemia or another growing blood-pollution, the ever- and everywhere-present depot for disturbing matter. So Hötzel's answer acknowledges the protein storage on basement membrane in times of hyperproteinemia.

We were most surprised and delighted by hearing Hötzel's statement as it is the acknowledgement of an important pillar of our doctrine, for which we wait since more than 30 years. So, unknown to us, the above explained physiological and pathological protein-storage apparently has been accepted in all secrecy as the new valid doctrine of nutrition.

*The healing therapy*

As storage is reversible, storage diseases are curable: Zero-diet for 4 weeks or protein-fasting for 1–3 months, accompanied by repeated blood-lettings, which work as protein losses, force regulations to take protein requirement for the body from the store.

Arterial endothelial cells now break off stored material from arteriosclerotic plaques, endothelial and epithelial cells of capillaries break off stored collagen from both sides of basement membranes, excreting it as amino acids and albumin into the blood and tissue fluid as nourishment for the cells. Arteriosclerotic plaques thereby fade, basement membranes regain their normal permeability. Elevated risk-factor blood-levels now lower to normal blood levels without further treatment. We use this therapy since 30 years with great success.

*Prophylaxis* against protein-storage diseases is attained by moderation in the consumption of animal protein: one meal every day vegetarian, one day every week vegetarian, one month every year vegetarian food only and beware of overnutrition, beware of gaining weight.

About protein-fasting and zero-diet many excellent descriptions have been published. A repetition is superfluous. Some reader, however, might be interested in the particular way of our treatment. Here it is: We hand out to each risk-factor patient at the beginning of treatment the following diet instruction:

*The protein-break-down diet as treatment for the alimentary micro- and macroangiopathy*

Dear patient: For 1–3 months you should not eat animal protein. As our body has a daily protein requirement of approximately 70 g, which vegetable protein only partially can substitute, metabolism is forced to take the rest of missing protein from the store. Thereby the overfilled store gradually empties and you regain your health. Strict vegetarian diet means: Vegetarian food only, nothing from animal! In particular: no meat, no meat products, no eggs, milk, milkpowder, cheese, yoghourt, cottage-cheese, fish, mussel, crab, lobster, nor other animals. Of the vegetarian food: no beans, peas, lentils, soja, nuts, as they are rich in vegetarian protein.

That diet is not suited for juvenile diabetics, children, pregnant women, and mothers with suckling, as those persons need a mixed food including animal protein of some kind.

Protein-break-down diet is not a nutrition for healthy persons, but a treatment for patients with overweight and hemoconcentration or risk factors or arteriosclerosis. This diet is suited for a limited time, 1–3 months, until health is restored. However, no housewife can for 3 months deliver, besides the meals for the family, an additional vegetarian meal for the patient. Therefore we make the following proposal:

The patient takes part in all meals of the family, thereby, however, omitting animal protein. Some examples: If for dinner goulash is served with potatoes, salad, and yoghourt with fruits, the patient leaves off meat and yoghourt. The rest of the meal is vegetarian: From the goulash, the patient eats potatoes with goulash gravy, salad, and fruits. From roast-pork with potatoes, the patient eats potatoes with pork gravy. For supper, the patient leaves off sausages, cheese, milk, and all other animal proteins. Instead he eats his slice of bread and butter with a tomato or a cucumber or a radish or a mixed salad. For breakfast, the patient eats no egg, sausage or cheese, but puts on his roll or bread marmelade or jam, thereafter some fruits or vegetables or juices made of them. Those meals contain 1. no animal protein and 2. less calories, both points being important for the obese risk-factor patient, as such restrictions break down not only the overfilled protein store, but also the overfilled fat store. Without having to starve, the patient grows healthy by that diet in 1–3 months. The unsalted diet should be composed to a great part out of raw, unboilded vegetables and fruits. The patient should not eat without hunger. Therefore he should not eat more than 3 meals a day, better 2 or even only one meal a day, as it is necessary that the patient has at some time of every day a strong feeling of hunger. Only by hunger the former continuous food storing of the body is reverted to a destoring, an emptying of stores. One day in a week there is juice fasting day, when only unsugared fruit and vegetable juices, almost free of calories, are allowed.

The following food-table 7 is a good adviser for the protein-fasting patient, who should omit all food with a protein content higher than 10 % (1st column of Table 7) and foodstuffs with more than 100 calories in 100 g (3rd column of Table 7). Patient shall drink much fluid during the time of fasting, at least 2 liters daily.

*Why is vegetable protein no factor in protein-storage diseases?*

Frequently the patient asks: What about the proteins in vegetables, don't they overfill the protein store? The answer is:

1. Meat contains about 5–10 times more protein than vegetables.
2. If a cell of our body is going to build up a human protein molecule, all amino acids, out of which the human protein molecule is composed, have to be present in the cell. If only one amino acid in the spectrum of amino acids is missing, no human protein molecule can be constructed. In that case, the cell uses the incomplete amino acids for energy production. As all vegetarian proteins have an incomplete amino-acid spectrum in relation to the human and animal protein, no human protein can be built up out of a single kind of vegetables. In some

Table 7. Proteins, fats, and carbohydrates in our food.

| From Documenta Geigy | 100 g edible substance containing | | | |
|---|---|---|---|---|
| | protein | fats | carbo-hydrates | calories |
| | g | g | g | kcal |
| apple | 0.3 | 0.6 | 15.0 | 58 |
| banana | 1.1 | 0.2 | 22.2 | 85 |
| pear | 0.5 | 0.4 | 15.5 | 61 |
| strawberry | 0.7 | 0.5 | 8.4 | 37 |
| cherry | 1.2 | 0.4 | 14.6 | 60 |
| orange | 1.0 | 0.2 | 12.2 | 49 |
| plum | 0.7 | 0.1 | 12.3 | 50 |
| grapes | 0.6 | 0.3 | 17.3 | 67 |
| grape juice | 0.2 | trace | 16.6 | 66 |
| lemon | 1.1 | 0.3 | 8.2 | 27 |
| cauliflower | 2.7 | 0.2 | 5.2 | 27 |
| beans | 1.9 | 0.2 | 7.1 | 32 |
| haricot beans | 21.3 | 1.6 | 61.6 | 338 |
| small peas | 6.3 | 0.4 | 17.0 | 84 |
| cucumber | 0.8 | 0.1 | 3.0 | 13 |
| carrot | 1.1 | 0.2 | 9.1 | 40 |
| potato | 2.1 | 0.1 | 17.7 | 76 |
| garden lettuce | 1.3 | 0.2 | 2.5 | 14 |
| kohlrabi | 2.0 | 0.1 | 6.6 | 29 |
| paprika | 1.2 | 0.2 | 5.3 | 24 |
| brussels sprouts | 4.7 | 0.4 | 8.7 | 47 |
| beet root | 1.6 | 0.1 | 9.9 | 43 |
| sauerkraut | 1.0 | 0.2 | 4.0 | 18 |
| asparagus | 2.1 | 0.2 | 4.1 | 21 |
| spinach | 3.2 | 0.3 | 4.3 | 26 |
| tomato | 1.1 | 0.2 | 4.7 | 22 |
| tomato juice | 0.9 | 0.1 | 4.3 | 19 |
| white cabbage | 1.4 | 0.2 | 5.7 | 25 |
| onion | 1.5 | 0.1 | 8.7 | 38 |
| champignon | 2.8 | 0.24 | 3.7 | 22 |
| chanterelle | 1.5 | 0.5 | 3.8 | 21 |
| peanut | 26.2 | 48.7 | 20.6 | 582 |
| walnut | 14.8 | 64.0 | 15.8 | 651 |
| flaked oats | 13.8 | 6.6 | 67.6 | 387 |
| rice | 7.5 | 1.9 | 77.4 | 360 |
| wheaten flour | 10.5 | 1.0 | 76.1 | 363 |
| wheat grits | 10.3 | 0.8 | 76 | 362 |
| crisp bread | 10.1 | 1.4 | 79 | 49 |
| rye bread | 6.4 | 1.0 | 52.7 | 227 |
| roll | 6.8 | 0.5 | 58 | 269 |
| cocoa | 19.8 | 24.5 | 43.6 | 299 |
| jam | 0.6 | 0.1 | 70.0 | 272 |
| sugar | 0 | 0 | 99.5 | 385 |
| margarine | 0.5 | 78.4 | 0.4 | 698 |
| oil | 0 | 99.9 | 0 | 883 |
| pale bear | 0.5 | – | 4.8 | 47 |
| wine | 0 | – | 0.2–8.0 | 60–120 |

vegetables the missing amino acids are the same, in others they are different. If one eats a mixed vegetable meal of the former vegetables, the meal is unusable for protein-production. If, however, in a meal of mixed vegetables different amino acids are missing, the different vegetables complete the amino-acid spectrum so that human protein can be built up by them. The reader finds combining and the not-combining vegetable compositions in L. and Th. Wendt: "Die essentielle Hypertonie der Überernährten", Frankfurt, 1938). In the protein-break-down diet only not-combining vegetables should be offered in each meal. If within 3 hours after the meal the missing amino-acids are not offered, the body cells cannot use the amino-acids for protein production. A patient who eats daily 3 meals and nothing between, that means the meals more than 3 hours apart, can nourish himself on not-combining vegetarian food so that his body is unable to gain protein out of that nourishment. Hunger is therefore not necessary for emptying overfilled protein stores. Nevertheless hunger is (3 weeks of zero-diet) the quickest way for its emptying.

*Blood-lettings*

The dietary protein-break-down can be accelerated considerably by repeated blood-lettings of 150–200 ml blood twice a week. For restoring the taken-away blood volume, one gives the patient the same amount of water to drink just after the blood-letting. Thereby the thickness of blood diminishes. Overnourished risk-factor patients always have thickened blood, with hematocrit mostly above 50 vol.%. 100 ml blood are composed of 50 ml water and 50 ml dry substance, mainly proteins. During a zero-diet an obese person loses (apart of fat) 60–70 g body-protein daily. With 3 blood-lettings of 200 ml each time in one week, the patient loses the protein equivalent of 5–6 days zero-diet.

Meanwhile the patient sticks to strict protein-fasting, which means that with the food hardly any protein comes into the blood, whereas the protein blood levels lower with each blood-letting. That induces endothelial cells of blood-vessel walls to break down collagen from basement membranes, transforming it into albumin and secreting it into blood stream for restoring its former composition. Thereby capillary basement membranes grow thinner and gain in permeability, while blood-protein levels slowly rise again. With the improved membrane permeability, the elevated risk factors begin to lower. The reactive refilling of blood-protein- and erythrocyt-losses by mobilization of stored protein gives the treating doctor the opportunity to continue blood-lettings until protein stores are sufficiently emptied. Basement membranes have now regained their physiological thickness and permeability, the blood its physiological viscosity and hematocrit (below 42 vol.%), all blood levels their normal heights, whereby the patient's health is restored.

*Prophylaxis and treatment of cigarette-smokers angiitis*

Prophylaxis consists in not smoking. As, however, this aim never will be attained, we must endeavour to reach the attainable. Two ways are open.

The pleasure for which the smoker smokes comes from nicotine. The poison of smoke, which produces angiitis and heart infarction, is carbon monoxide. The cancer comes from the tar products in the smoke. Both poisons develop from the incomplete burning-process in smoking, the burning without flames.

1. One can get the pleasure of nicotine without the poisonous smoke if one uses chewing*) or sniffing tobacco. Both ways of nicotine intake bring the whole pleasure of nicotine without any danger of later harm by cancer or heart infarction, as by chewing or sniffing no smoke develops and nicotine in such doses is not poisonous as it does not accumulate, but is excreted totally every day by the kidneys.
2. On the other hand, one can detoxicate the cigarette smoke by inspiring the smoke through a hopcalit filter. Hopcalit is a manganese oxide mixture. It oxidizes carbon monoxide into the unpoisonous carbon dioxide by catalysis. It is used in the army, navy, and fire-brigades of all countries since World War I against carbon-monoxide poisoning with reliable success. That it works also in cigarette filters oxidizing all carbon monoxide in cigarette smoke we published 1973 in: L. Wendt: „Krankheiten verminderter Kapillarmembranpermeabilität".

**Therapy of multifactorial angiopathies**

The recognition of the different disturbing substances in the blood (Tables 3–6) is of importance for the therapy. Patients with micro- and macroangiopathies have a lysosomal weakness of endothelial and epithelial cells. By large quantities of disturbing proteins, their breaking-down power is overburdened. They cannot break down all of them. They let pass the unbroken rest on capillary and arterial walls, which leads to angiopathies. If the treating doctor puts such a patient on protein fasting-diet, the onflow of surplus *food* protein *ceases.* That is a great alleviation for the lysosomal enzymes of endothelial cells. They may be able now to break down the rest of the disturbing proteins so that the patient is growing healthy. The same effect has zero-diet (L. E. Trang et al., 1979). In other patients, protein-fasting is not enough. It leads only to an improvement of the disease, but not to healing.

If now the doctor succeeds in stopping the patient's smoking, carbon-monoxide hemoglobin disappears out of blood. The amount of disturbing proteins, which enzymes of endothelial cells have to breake down, is again considerably reduced thereby, which means healing for another percentage of such patients. But in some cases the disease goes on, nevertheless, the patient having nothing but a hyperantigenemia. The hyperantigenemia is the etiology of rheumatoid arthritis, lupus erythematodes, and many other autoimmun diseases, which we call antigenopathies, as almost all of them are caused by bacterial or viral antigen. The hyperantigenemia can be treated successfully by plasma-exchange (P. Reuther 1980, U. Rother1980, E. Rümpl 1980, W. M. Glöckner 1980, Jahresversammlung Dtsch. Ges. Neurologie, Wiesbaden 1980), plasma-phoresis (L. Wendt 1973, 1980. P. E. McKenzie et al. 1979) and by blood-plasma filtration. Antigen-antibody complexes are big molecules. By filtration of blood

*) In England a nicotin chewing gum is on the market.

plasma through an appropriate filter, those molecules get trapped in the filter, the blood, reflowing into the patient, being almost free of them.

The free antigen in the blood, however, is a much smaller molecule than the antigen-antibody complex. The pore filter is therefore not suitable for cleaning the blood from antigen. However, the free antigen has (at its determinated flat) an electromagnetic polarization. If we pass the blood-plasma of the patient a second time through a filter, the pores of which have a polarization opposite to that of the antigen, the antigen will be bound in the filter by magnetism. After those two filtrations, the blood pollution by antigen and antigen-antibody complexes is conspicuously reduced, the hyperantigenemia is transformed into a hypoantigenemia, which even a patient with weak break-down enzymes can easily keep under control. Now even those patients grow healthy.

The pore filter for cleaning the blood from antigen-antibody complexes has been constructed already and has approved in patients with rheumatoid arthritis and other autoimmunity diseases. American doctors report of great improvement in such patients after plasma-filtration. In spite of not knowing what they take out of the blood by filtration, they are sure that it must be some matter which is the cause of those diseases (Y. Nose 1979, L. and Th. Wendt 1978/79).

*Summary*

*The physiological storage in overnutrition with mixed food*

Our food passes after digestion in the bowels through the mucous membranes of bowels into the blood. Thereby each meal of a mixed food produces an elevation of the blood level of all food molecules: a hyperalbuminemia, a hyperglycemia, a hyperlipemia, a hyperhydremia. Those high blood levels of food molecules and water produce equivalent high diffusion and filtration pressures. In connective tissues those pressures are low. So food molecules according to pressure differences flow downstream through capillary basement membranes (BM) into tissues. Having arrived there, cells take their requirement. From the surplus food, protein is stored in collagen and amino groups of mucopolysaccharide of connective tissue, glucose goes into the sugar part of mucopolysaccharide, fat goes into the fat cells of connective tissues, water goes into the domain of mucopolysaccharide. So each food-transport molecule (water-soluble) has its food-storage molecule (water-unsoluble) in connective tissue.

In hunger, regulations take the albumin out of collagen and amino groups of mucopolysaccharide, the glucose out of sugar part of mucopolysaccharide, the fatty acids out of fatcells, the water out of the domain of mucopolysaccharide. Thereby connective tissue is the physiological foodstore of all food molecules. As long as that physiological storage of surplus food molecules functions undisturbed, the person may grow fat, but stays healthy.

*The pathogenic food storage*

The capillary basement membrane (BM) is the bottle neck of protein-transport channels. Its pores have diameters between 28 and 70 Å. All food molecules have considerably smaller diameters than the smallest BM pores except albumin (Ø 38 × 150 Å). The occlusion of small BM pores by albumin transport therefore is a continuous physiological filter process, which is compensated by a simultaneous continuous filter change, performed by the capillary endothelial and epithelial (EE) cells.

If, however, the protein overnutrition is so great that EE cells cannot speed up enough the filter-change or if the person has a functional weakness of protein building-up and breaking-down enzymes of his EE-cells, which prevents a quicker

filter change, occlusion of basement-membrane pores increases, its permeability diminishes. That hinders above all the big albumin molecules in their BM passage. Albumin dams up, its blood level rises, there is danger of hyperoncia and hyperviscosity. Endothelial cells, the guardians of blood, interfere. They take surplus albumin out of blood, change it into storage protein (collagen) and depose it on BM. Thereby blood becomes thinner, BM thicker. That is the pathogenesis of BM thickening in risk-factor patients. The damming up of food molecules before thickened BM increases their blood levels, lowers their filtration and diffusion rates into tissues, diminishes cell nutrition. Regulations compensate that disturbance by elevating the blood levels of dammed-up molecules to that height, from which diffusion and filtration pressures arise, high enough for overcoming the permeation retardation of thickened BM.

The suchlike increased capillary filtration pressure is the pathogenesis of essential hypertension, the increased capillary diffusion pressure by hyperglycemia is the pathogenesis of adult diabetes, other risk factors rise accordingly.

All dammed-up molecules in blood act disturbingly. Capillary endothelial cells resorb them, storing them on BM. Sooner or later, BM gets overfilled by them, BM cannot take in further storing molecules. In consequence, blood levels of dammed-up molecules rise again, overstepping the threshold of those endothelial cells, which are located on arteries. Their storing material (albumin, lipoprotein and all other dammed-up molecules), however, goes on the intima of arteries, producing the arteriosclerotic plaque. So alimentary arteriosclerosis is a storage disease, caused by pathogenic protein storage.

*Prophylaxis of hematogen angiopathies*

If man would keep his environment clean, most of his present blood pollutions (for instance by lead, cadmium, carbon monoxyde, nitrosamine, and many others) would disappear and with them many of his present diseases. More than 50 % of all premature deaths are caused by cardiovascular diseases (G. Schettler, 1978), only 25 % by cancer, and the last 25 % are the deaths of all other diseases including traffic accidents. Micro- and macroangiopathies are the last undefeated plagues of our time, the most deadly disease of all, double as deadly as cancer, its frequency still growing, cure unknown. Of those premature cardiovascular deaths, 90 % have their origin in overnourishment and cigarette smoking. Those patients lose half of their lifespan, dying in their prime of life. They can be cured so that they might live to their physiological life expectancy in great age.

*The healing therapy*

As storage is reversible, storage-diseases are curable: Zero-diet for 4 weeks or animal-protein fasting for 1–3 months, encouraged by repeated blood-lettings, which work as protein losses and force regulations to take protein from the store; endothelial-epithelial cells break off collagen from intima of arteries and capillary basement membranes, which regain thereby their normal permeability. Elevated risk factors lower now to normal blood levels without further treatment. We use this therapy since 30 years with great success (L. Wendt, 1949).

*Zusammenfassung*

*Die physiologische Verstoffwechselung einer überkalorischen Mahlzeit mit gemischter Kost*

Die im Darm verdaute Nahrung tritt ins Blut und erzeugt einen Anstieg der Blutspiegel aller Nährstoffmoleküle, das heißt eine Hyperalbuminämie, eine Hyperglykämie, eine Hyperlipämie und eine Hyperhydrämie. Von diesen hohen Nährstoffblutspiegeln gehen entsprechend hohe Diffusions- und Filtrationsdrücke

aus. Jenseits der Kapillarwand, im Bindegewebe, sind diese Drücke niedrig. So strömen das Wasser und die in ihm gelösten Nährstoffmoleküle mit dem Druckgefälle stromabwärts in den Geweberaum. Dort decken die Zellen aus dem Nährstoffangebot ihren Bedarf. Von dem verbleibenden Überschuß wird Eiweiß gespeichert im Kollagen und in der Aminogruppe des Mukopolysaccharid des Bindegewebes, die Glukose im Mukopolysaccharid des Bindegewebes, das Fett in den Fettzellen des Bindegewebes, das Wasser in der Domäne des Mukopolysaccharid des Bindegewebes. So hat jedes Nährstoff-Transport-Molekül (wasserlöslich) sein spezifisches Speichermolekül (wasserunlöslich) im Bindegewebe. Im Hunger entnehmen die Regulationen dem Kollagen des Bindegewebes das Albumin, dem Mukopolysaccharid des Bindegewebes das Albumin, die Glukose und das Wasser, den Fettzellen des Bindegewebes das Fett. So ist das Bindegewebe der physiologische Nährstoffspeicher für alle Nährstoffe. Solange diese physiologische Verstoffwechselung der Nährstoffe andauert, führt eine Überernährung durch Füllung des Bindegewebsspeichers zu Übergewicht aber nicht zur Krankheit.

*Die pathogene Nährstoffspeicherung*

Die Kapillarbasalmembran (BM) ist der Engpaß der Eiweißtransportwege. Ihre Poren haben Durchmesser zwischen 28 und 70 Å. Alle Nährstoffmoleküle haben beträchtlich kleinere Moleküldurchmesser als die kleinsten BM-Poren mit Ausnahme des Albumins (Ø 38×150 Å). Die Verstopfung der kleinen BM-Poren durch den Albumintransport ist also ein kontinuierlicher physiolischer Filterungs-Prozeß, der durch den kontinuierlichen Filterwechsel, den die Endothel- und Epithel-(EE)Zellen der Kapillarwand vollziehen, kompensiert wird. Ist aber der Eiweißverzehr und dadurch der Albumintransport durch die BM zu stark oder besteht eine Funktionsschwäche der Eiweißaufbau- und Eiweißabbau-Enzyme der EE-Zellen, so daß der Filterwechsel der BM nicht genügend beschleunigt werden kann, dann verstopft die BM mehr und mehr und büßt dadurch an Permeabilität ein. Das behindert zunächst die MB-Passage des Albumins, es staut ins Blut zurück, sein Blutspiegel steigt. Die dadurch entstehende Gefahr einer ansteigenden Hyperonkie und Hyperviskosität bannen die Kapillarendothelzellen, indem sie Albumin aus dem Blut nehmen und es als Kollagen auf der BM speichern. Dieser Speicherungsprozeß verdünnt das Blut, verdickt aber die BM. Das ist die BM-Verdickung der Risikopatienten. Mit dem Quadrat der BM-Verdickung verlängert sich die Diffusionszeit aller die BM permeierenden Nährstoffmoleküle, mindert sich ihre Diffusionsrate in der Zeit, diese Moleküle stauen ins Blut zurück, so daß die Zellversorgung sinkt. Die Rückstauung der Nährstoffmoleküle und mangelnde Zellversorgung kompensieren die Regulationen dadurch, daß sie die Blutspiegel der permeationsverzögerten Nährstoffmoleküle solange erhöhen, bis die von ihnen ausgehenden Diffusionsdrücke groß genug sind, die Diffusionsgeschwindkeit bzw. -menge durch die verdickte BM so zu steigern, daß wieder physiologische Diffusionsraten der Nährstoffmoleküle ins Gewebe strömen, wodurch die physiologische Zellernährung wieder gesichert ist. Die bei diesem Prozeß auftretenden Blutspiegelerhöhungen sind die Risikofaktoren und die Krankheiten der Überernährten: Bluthochdruck, Erwachsenendiabetes, Hypercholesterinämie, Gicht. Die erhöhten Blutspiegel der rückgestauten Moleküle wirken als Blutstörstoffe. Die Endothelzellen, die Wächter über die Blutreinheit, nehmen die Blutstörstoffe aus dem Blut und speichern sie zusammen mit dem rückgestauten Albumin auf der BM, die dadurch schließlich überfüllt wird und keine Speichersubstanzen mehr aufnehmen kann, so daß die Blutspiegel der Stauungsmoleküle wieder ansteigen. Schließlich übersteigen sie den Schwellenwert der Endothelzellen, die auf den Arterien sitzen. Sie scheiden nun die rückgestauten Moleküle (Eiweiß, Lipoproteine, Glukose usw.) auf die Intima der Arterien. Das ist die Pathogenese der alimentären Arteriosklerose, ihre Ursache ist die pathogene Eiweißspeicherung auf der BM, sie selbst eine Eiweißspeicherkrankheit.

*Die Prophylaxe der alimentären Angiopathien*

Alimentäre Angiopathien treten nicht auf, wenn man die Überernährung mit tierischem Eiweiß vermeidet. Das ist erreichbar, wenn man im täglichen Alltag Maß hält, einerseits die Überernährung vermeidet, andererseits jeden Tag eine vegetarische Mahlzeit, jede Woche einen vegetarischen Tag und jedes Jahr einen vegetarischen Monat einhält.

*Die naturgemäße Therapie der alimentären Angiopathien*

Da Speicherung reversibel ist, sind Speicherkrankheiten heilbar: 1. Beendigung der Fleischmast und Erzeugung eines Eiweißmangels durch Fleischfasten oder Nulldiät. Dadurch werden die Regulationen gezwungen, den Eiweißbedarf des Körpers dem Speicher zu entnehmen.

2. Behebung der Eiweißüberlastung des Blutes (Hämokonzentration) durch wiederholte Aderlässe; das bedeutet zugleich Erzeugung von Eiweißverlusten, die den BM-Speicherabbau beschleuningen.

3. Fortsetzung dieser beider Maßnahmen, bis die Überfüllung des BM-Eiweißspeichers abgebaut und die normale Permeabilität der Basalmembranen wiederhergestellt ist. Die erhöhten Blutspiegel der Risikofaktoren sinken dann ohne weitere Behandlung von selbst zur Norm. Diese Therapie ist um so wirkungsvoller, je früher sie einsetzt. Sie sollte begonnen werden bei jedem Übergewichtigen mit Symptomen der Hämokonzentration.

*Key words:* arteriosclerogenesis, capillary basement membrane thickening, heart infarction, protein storage, risk factor diseases

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