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Editorial

Arteriosclerosis Without End*

Principles of Pathogenesis and an Attempt at a Nosologic Classification

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Summary. 1. The duration of systole, the pulse-wave-velocity and the dimensions of the cardiovascular system (length and lumen of arteries) are optimally coordinated, in a species–specific manner.

2. The physiological properties of human arteries are consistent only if the product of systolic duration and pulse-wave-velocity is constantly related to the length of the arteries.

3. The main functions of human arteries are material-transport, -distribution, and -exchange. All potential changes will affect these properties and result in an insufficient blood supply.

4. Arteriosclerosis is not a nosologic entity but a complex of morphological findings resulting from both exogenous and endogenous conditions.

5. Knowledge of the morphogenesis of certain changes does not necessarily suggest the pathogenesis, "Erkenntnisgrund" (cognition) and "Realgrund" (reality) are different.

6. It appears that one can differentiate two main types of arteriosclerosis and four "Gangarten" (modes of progression) which can be differentiated with certainty if the following data are known:

a) biorheutic processes (ageing of vessel-wall-layers),

b) morphologic findings (oedema as a result of plasmaseepage into the wall; cell proliferations),

c) course of once initiated changes,

d) prognosis and therapeutic response.

7. The majority of arteriosclerosis–forms are related to a disturbance of the seeping of bloodplasma *"a corde in peripheriam et ab intima in adventitiam"*.

* After impressions during the French-German meeting of pathologists, Munich 18th of March 1978

** Dedicated to Prof. Dr. Dres. h. c. med. D. Litt. h. c. Walter Pagel, London, to his 80th birthday (12th November 1978) in affectionate reference

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8. Uncommon types develop as intimal proliferations with secondary changes.

9. Those forms which show an increased incorporation of fibrin and fibrinogen into the arterial wall via the intima and those with an increased platelet–aggregation are like v. Winiwarter-Buerger's disease ("inflammatory arteriosclerosis").

10. The endothelium of the arterial intima occupies a key position. If it is intact, significant arteriosclerotic changes are unlikely to develop. If it is defective or highly permeable, proliferations of the smooth muscle cells (Langhans-cells) are induced by various factors including some derived from platelets.

Key words: Arteriosclerosis – Benign and malignant type – Perfusion – Intimal cell-proliferations.

There have been world-wide efforts to explain the various findings of arteriosclerosis by their *morphological* manifestations and to understand their *causation.* More questions have been raised than answers provided. Usually authors overemphasiz their own points of interest as key-findings and hus everybody keeps *"his"* arteriosclerosis and speaks *"his"* language, – *optima fide.*

I have therefore attempted:

1. to remind the morbid anatomists of some *facts,*
2. to emphasize the importance of commonly occuring *findings,*
3. to characterize the *prevailing* pathogenetic *principles.*

Hubert Bouissou (Toulouse) and his coworkers have taken the view that the process of ageing in human skin is unexpectedly similar to those of the aortic wall. Ageing of certain scleroproteins were *one* condition of the onset of arteriosclerosis. This view-point seems so remarkable that it is worth-while thinking about certain *fundamental premises:*

Circulation *serves* metabolism (Siebeck, 1974). In the circulatory system there are four structures involved in material-transportation, the heart and arteries, terminal vessels and veins. All have *one* principle of construction: they consist of "endothelium" and "accessoria". The type of vessel is determined by the latter and the structural variation of the accessoria is great.

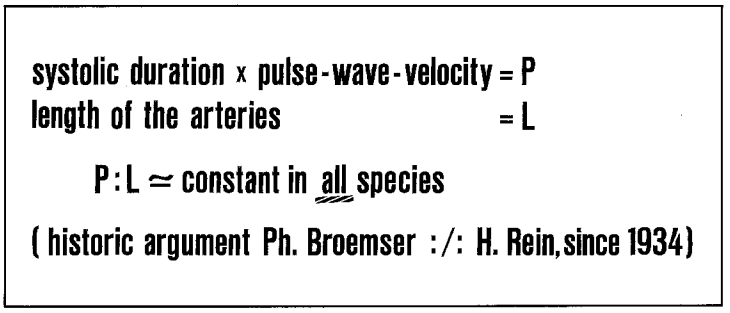

Fig. 1

Under normal conditions there are optimal relationships between the duration of systole, pulse-wave-velocity and the dimension of the blood-vessel-system (Fig. 1). These are *species-specific* and secure maximal blood transportation (Ph. Broemser, 1934; critique at Th. Kenner, 1967). The product of the duration of systole and pulse-wave-velocity is in a quite constant relationship to the length of the arteries in all classes of vertebrates. Any disturbance of this interesting and complex situation is followed by certain sequaelae which constitute the pathology of the blood-vessel-system.

What is the length of all the arteries in *man*? Nobody knows for certain, Sir Charles Bell published in the year 1819 – the year when the first chair of morbid anatomy[1] was established[2] – a paper about his "artery-man"[3]. The weight of the arteries shown[4] was similar to that of the heart. The critical weight of the two synergists – heart and arteries – is at 500 g each. In the blood-vessel-system there are general pathological manifestations ("General pathology" Fig. 2).

According to Anitschkow (1925) the main properties of arteries are: contractility, elasticity and permeability, to which I have added material-*transportation,-distribution* and *-exchange* (Doerr, 1975). All pathological derangements have an influence on these properties. The clinically predominant symptom is an inadequate blood supply (Fig. 3). There are three groups of causes for this disturbance, but in practice one finds combinations of all three. The following figure (Fig. 4) illustrates several problems.

The endeavour for clarification of the nature of arteriosclerosis reminds us of an automatic process: If the program is wrong, the resulting data do not fit for a general theory.

It is as J.W. Goethe says:
"*Wer den ersten Knopf falsch knüpft, kommt mit dem Zuknöpfen nie zurecht!*"
(If the initial step is false the whole journey will be out of true).

Arteriosclerosis is not a nosologic entity. It is a complex of morphological findings, which is the result of various constitutional changes and exogenous disturbances. The identification of the *early stages* of arteriosclerosis is the key for the understanding of its morphogenesis. This view is taken by Wg. Rotter (1978) and Sinapius (1978). Arteriosclerosis is not only the response of the arterial wall to a series of changes in general metabolism and certainly not simply a response to changes in the vessel-wall-metabolism. The morbid anatomy of arteriosclerosis shows heterologous characteristics and its analysis is an excellent challenge for a conditionalistic point of view.

From this point of view one notices quickly that there are different patterns of arteriosclerosis with different initial changes. Arteriosclerosis shows two *general patterns* (types) and some variations. We called the variations "Gangarten" (modes of progression; 1964) which can be characterized by the following factors:

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1 The first chair of pathology, "the world has seen" (W. Fischer and G.B. Gruber, 1949)
2 Joh. Friedr. Martin Lobstein d. Jüngere, Strasbourg
3 Published at W. Doerr, 1963, Vol. II, p. 895
4 All those arteries which one can dissect "by hand"

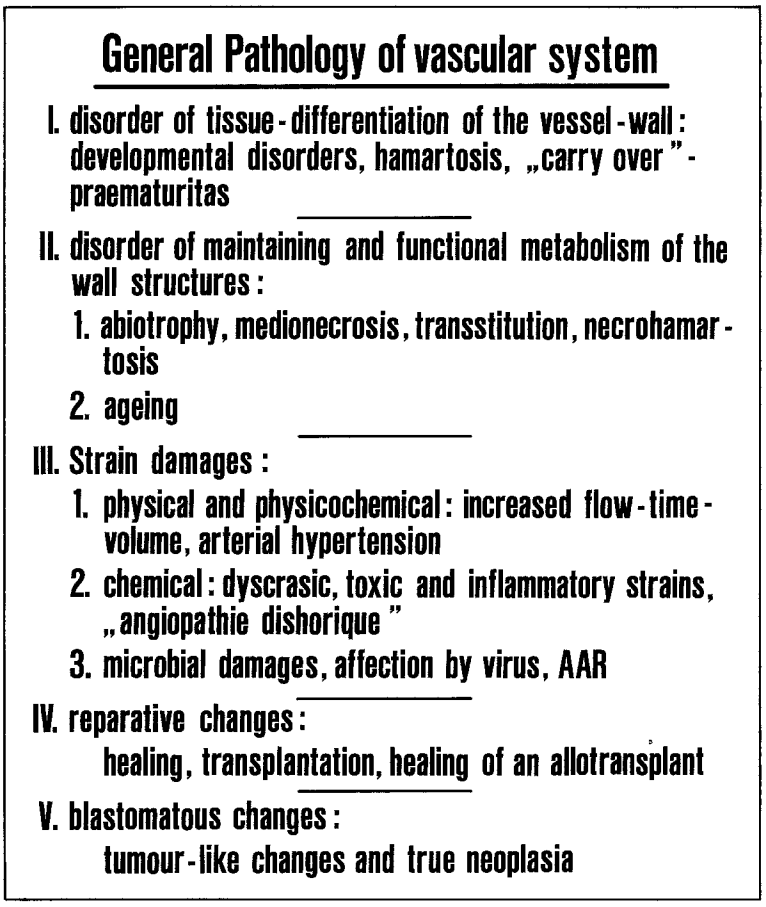
General Pathology of vascular system
I. disorder of tissue-differentiation of the vessel-wall: developmental disorders, hamartosis, „carry over"-praematuritas
II. disorder of maintaining and functional metabolism of the wall structures:
1. abiotrophy, medionecrosis, transstitution, necrohamartosis
2. ageing
III. Strain damages:
1. physical and physicochemical: increased flow-time-volume, arterial hypertension
2. chemical: dyscrasic, toxic and inflammatory strains, „angiopathie dishorique"
3. microbial damages, affection by virus, AAR
IV. reparative changes:
healing, transplantation, healing of an allotransplant
V. blastomatous changes:
tumour-like changes and true neoplasia

Fig. 2

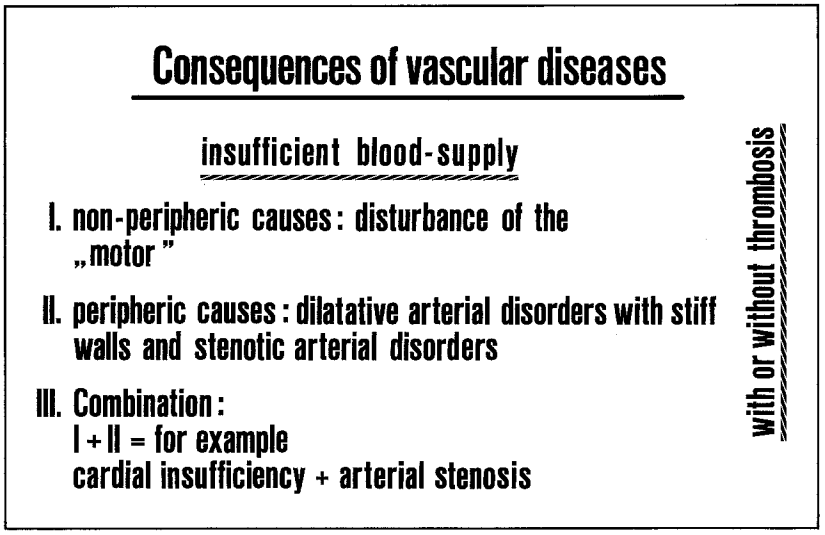
Consequences of vascular diseases
insufficient blood-supply
I. non-peripheric causes: disturbance of the „motor"
II. peripheric causes: dilatative arterial disorders with stiff walls and stenotic arterial disorders
III. Combination:
I + II = for example
cardial insufficiency + arterial stenosis
with or without thrombosis

Fig. 3

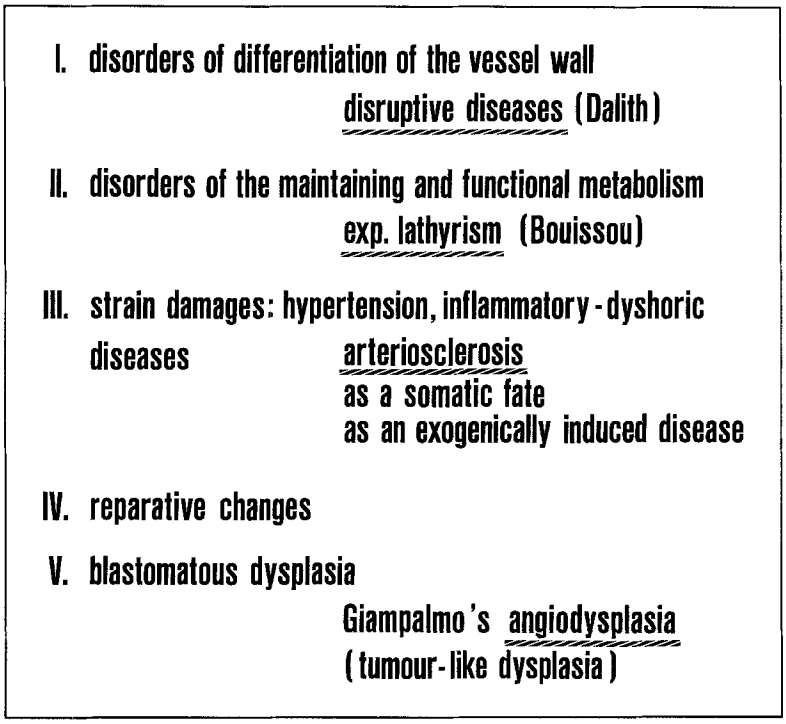

Fig. 4

1. Changes due to and associated with ageing,
2. morphological findings,
3. different rates of progression of once initiated changes,
4. prognosis and therapeutic assessment.

We differentiated the following manifestations (Fig. 5): Obviously there are two main types, a "benign" and a "malignant"—a more dangerous—one.

There are three variations of the benign type:

1. The harmless physio-sclerosis (Bürger, 1967; Moschetto et al., 1974; critique at Krug, 1976);
2. a form, which shows marked incorporation of fibrin-components and later microthrombosis (Rokitansky, 1844, 1856; Duguid, 1946; Bleyl, 1969; Baumgartner, 1977);
3. Atherosclerosis or scleratheromatosis (Förster, 1873; Marchand, 1904).

The *malignant type* is characterized by disseminated intimal proliferations, oedema rich in proteoglycanes, and necrosis. Cut the pip of a lemon into halves at the equatorial plain and put one piece between intima and media so that the convexity is situated at the luminal side: you have a "clear" plaque. Subsequently the plaque may become an atheroma.

The "benign" type of the arteriosclerosis is characterized by longitudinal oedema at the intima-media-junction—in the aorta up to 30 cm of length,—whereas the "malignant" type shows focal-circumscribed plaques which may be subject to secondary changes.

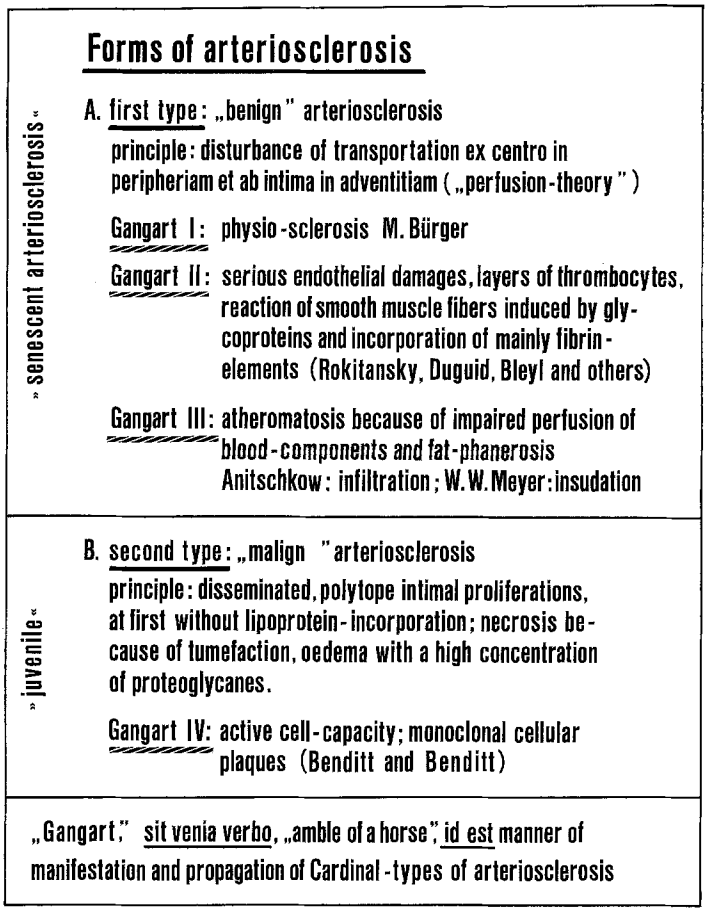

Fig. 5. Compilation of the types and Gangarten (modes of progression) of arteriosclerosis (according to principles of classification by Doerr, 1963, 1964, 1970), "senescent" means these arteriosclerotic forms occur in each individual, if he gets sufficiently old; "juvenile" means that these types are more common in younger people than in older. Pathogenetically there is a disturbance of perfusion in Gangart I–III (first type = "benign" sclerosis), whereas in Gangart IV (second type = "malignant" sclerosis) there is a connection to cellular proliferation

Two interesting facts may be pointed at:

(1.) It is a common error to believe that "arteriosclerosis" always begins "focally". In contrast the most common forms of arteriosclerosis (Gangarten I to III) are generalized with extensive oedema within the deep intimal layers, like a cylinder jacket. Those who doubt this should use the holoptic technique of aortic sectioning which I have repeatedly used (1963).

"Focal" changes in these forms of arteriosclerosis are secondary to endothelial defects, intimal ulceration, plasma-seepage and organisation of microthrombi etc.

(2.) The term "atheroma" is ill defined (Doerr, 1970), the history of the term is quite old (Lobstein, 1833; Gluge, 1843; Risse, 1854; Hofer, 1974).

Somehow it implies "fatty degeneration", either by "deposition" or "phanerosis".

As everybody knows there are many views on the pathogenesis of arteriosclerosis, but there are only three historic theses:

1. C. v. Rokitansky discussed "protein body-incrustation" (1844, 1846, 1856);

2. Virchow defined "endarteritis chronica deformans", as a certain type of parenchymatous inflammation, (1854);

3. the Russian school under the leadership of Anitschkow suggested that arteriosclerosis is atheromatosis, that is, a result of seepage of plasma into the intima with secondary changes ("infiltration"). This hypothesis followed the results of experimental feeding of cholesterol in sun flower oil.

All these theses are correct in some respects but cover different findings. Virchow's "inflammation" must be interpreted as a tissue-reaction[5]. The conceptions of Rokitansky and Anitschkow do not differ in principle. Both conceptions imply that the "materia peccans" is "incrusted", (infiltrated), from the blood by a pressure gradient. We suggested that material perfuses "*ex corde in peripheriam et ab intima in adventitiam*" and that most forms of arteriosclerosis might be explained by disturbance of this material-transport.

The *processes of transportation* depend on various factors, the pore-size of the molecular filter formed by the ground substance (Iverius, 1973; Buddecke, 1974, 1977), the nature of the endothelium, and the morphological singularity of the elastic-muscular mesenchyme of the deep intima and media. A *triad of causative factors* may be pointed out: blood-factor, barrier-factor and wall-factor determine the morphogenesis of arteriosclerosis.

For better understanding an example of each Gangart (mode of progression) is given:

A) In febrile diseases, but also in other conditions, the aorta shows oedema of the intima (Fig. 6a). It is caused by seepage through the inner surface of the vessel and by disturbance of the transport of fluid in the wall ("congestion"). Meessen et al. (1975) reproduced this congestion of material by sheathing a rabbit aorta into plastic tubes. After several weeks a diffus arteriosclerosis was seen. *Gangart I.*

B) If one examines the surface of an aortic resection-specimen by semithin-sectioning one finds a homogenous fibrin-agglomeration surrounded by a cellular population (Fig. 6b). There is no doubt that small amounts of fibrin and some of its components are incorporated permanently. One finds "lawns" of thrombocytes where endothelial cells are lacking. If this continues fibrin incrustation becomes remarkably severe. This may be a mode of formation of atheroma. *Gangart II.*

C) An exceptional scleratheromous manifestation occurs when diabetes mellitus, familial hyperlipidaemia and a "rich diet" is involved. This is what you could call "atherosclerosis" (*sit venia verbo*). There is a high concentration

[5] To appease the balance of the tissues. *In German*: Entzündung im Sinne Virchows bedeutet die Summe aller Vorgänge, die geeignet sein können, ein verlorengegangenes gewebliches Gleichgewicht wiederherzustellen

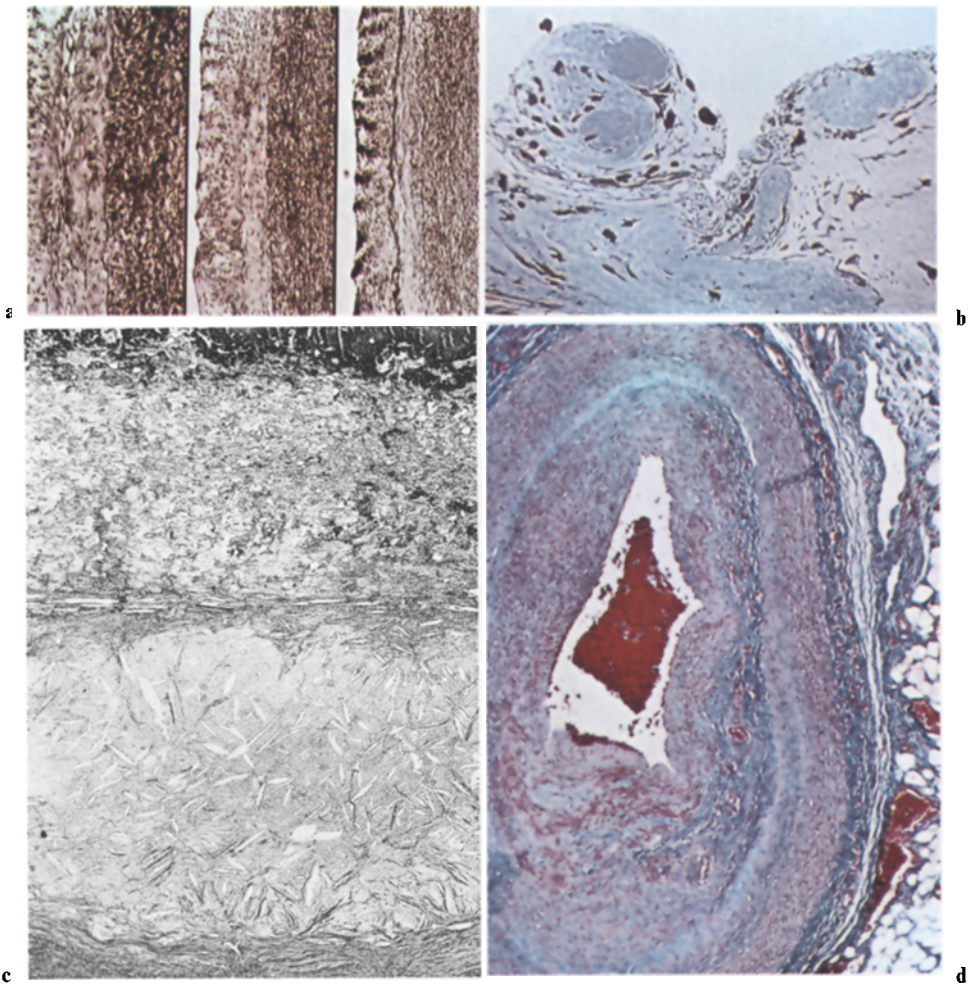

Fig. 6a–d. Compilation of representatives of each Gangart (mode of progression). **a** First Gangart, longitudinal section of aortic segment, longitudinal oedema at the intima-media-junction of the aorta; functional structures of the aortic surface, seepage of liquid through the elastic layers into the media. Paraffin, HE microphotograph, magnification 20:1, 65:1, 140:1. **b** Second Gangart, aortic surface, resection-specimen because of aortic coarctation, araldite-embedding, semithin-section, macroscopically: smooth aortic surface; microscopically: incorporation of fibrin-balls ("blue") into the intima; continuous incorporation with intimal thickening. Giemsa, microphotograph, magnification 860:1. **c** Third Gangart, atheromatosis, seepage of lipoproteid-components from the circulating blood to all layers of the media via intima. Accumulation because of impaired perfusion; 52 year old, male, diabetes mellitus, abdominal aorta, frozen section, microphotograph, magnification 25:1 Haemalaun-Sudan. **d** Fourth Gangart, juvenile coronary sclerosis, excentric intimal proliferation, mainly on the lower border of the photograph, fresh parietale microthrombosis, cellular intima-growth, no fat-deposits, paraffin, Masson-Goldner, 36 year old, male, microphotograph, magnification 320:1.

of fat-protein compounds (Fig. 6c), and one may see a cellular proliferation *or* a necrobiosis depending on the lipoproteins (Bailey, 1973; Doerr, 1976). *Gangart III.*

D) The second type of arteriosclerosis according to our classification (Fig. 5) is not concerned with transport and perfusion. I call it the "malignant" type because of its poorer prognosis. It may occur in the second or third decade of life, with a gradual progression. In the case of the juvenile coronary sclerosis it is "a play in one act". A. v. Albertini after investigating sudden deaths of Swiss soldiers during the last war (1943) described "arteriitis stenosans coronariae" with a formation of small thrombi on intimal cushions (Fig. 6d) which are a reaction to earlier "lawns" of thrombocytes. The cellular proliferation decides the fate of the disease. If the process temporarily stops – but this is exceptional – a fibrous cap-like scar is formed. *Gangart IV.*

In Germany these changes have been described by Meessen (1941), Wg. Rotter (1949, 1958), Erich Müller (1949), Heinrich Bredt (1949) und Doerr (1964). It has always been clear that it is not a common manifestation, as the proliferative tendency is unmistakable. The victims of this type of vessel-sclerosis are predominantly young men, cigarette smokers, who have suffered from a common cold or an upper respiratory tract infection 2 to 4 weeks prior to death.

Two facts must be kept in mind:

1. that different forms of arteriosclerosis are initiated by different mechanisms;

2. that if one knows the morphogenesis of certain changes, one does not necessarily understand the pathogenesis, *"Erkenntnisgrund"* (cognition) and *"Realgrund"* (reality) are different matters.

The survey of the initial lesions of the "Gangarten" (Fig. 7) emphasizes that each form of arteriosclerosis has its own particular "history": Gangart I, II and III are caused by a disturbance of plasma perfusion; Gangart IV is caused by intimal cell-proliferation. Gangart II and IV bear a relationship to a basic inflammatory mechanism. Mild courses of v. Winiwarter-Buerger's disease are the prototypes of Duguid's sclerosis. Juvenile sclerosis may be interpreted as "serous-cellular inflammation" (Rössle, 1934, 1943).

The mechanism of transmural material-transportion ("perfusion") depends on several factors: *the function of the endothelium* (Landau, 1913; Bleyl and Wegener, 1969; Schwartz and Benditt, 1972; Björkerud et al., 1972; Lang, 1974; Constantinides, 1974; Kurozumi, 1975; Schaper et al., 1976; Russell Ross et al., 1977; Christensen and Nielsen, 1977; Hammersen, 1978), *the size of the molecular filter of the proteoglycan – enriched ground substance* (Hauss, 1972; Moschetto et al., 1974; Jellinek and Elemer, 1976; Orcel and Bouissou, 1976) *alignment of the scleroproteins* (Bouissou et al., 1973; Nemetschek, 1974; Bouisson et al., 1974; Douste Blazy et al., 1976; Riedl and Nemetschek, 1977), *reactivity of the cellular components of all wall layers* (Fuchs, 1977) *and integrity of the venous side of the vasa vasorum and of the lymphatics within the adventitia* (Doerr, 1974, 1975, 1976). The cellular reaction involves those cells of the intima which were described by Rokitansky (1856) and Langhans (1866). Wissler (1968, 1974a, b), Haust (et al., 1965, 1972; Haust and More, 1972) and Knieriem (1960) showed that they are smooth-muscle-type cells, which are able to phagocy-

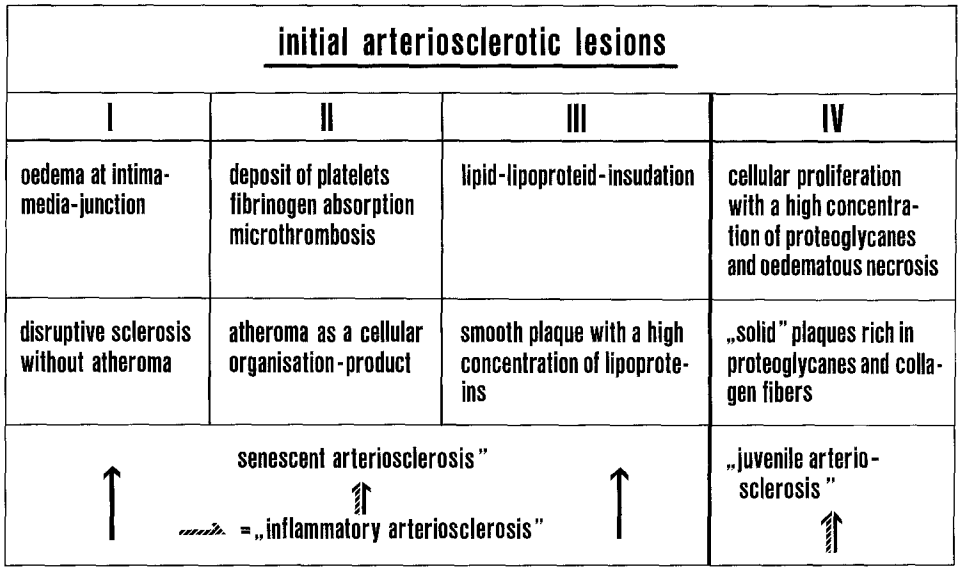

Fig. 7

tose material (*material absorption*), to secrete (*material release*) and to proliferate (*regeneration*). The foam-cells of the mucous-membrane in gastritis and the pseudoxanthome-cells of the myometrium in gestosis, too, are referred as myocytes. Our Langhans-cells and Wissler's myocytes have induced a great literature (Ross and Glomset, 1976; Wissler, 1977, 1978a, b; Ross 1978). Pott and Staubesand (1977) differentiate between "contractile" and "modified" myocytes. These cells do the main work of forming plaques and atheromas and they are subject to certain *regulation-mechanisms.*

We have the following conception on the nature of these regulation-mechanisms:

1. Baumgartner (1963, 1977) and Baumgartner and Studer (1978) showed that endothelial lesions are covered by thrombocytes and that in this condition a hormone-like, heat-stable glycoproteinbody with a molecularweight of 13.000 is released and that this glycoproteinbody induces the adjoining myocytes to grow. These authors conclude that if the endothelium could be protected against injury for example by hypertension, hyperlipidaemia, homocystinaemia etc. there would be no pathological effect. On the other hand we have to consider that an increased platelet-aggregation (for example in cigarette-smokers, increased blood-level of CO, release of catecholamines) may induce a thickening of the intima and so form a stenosing, even obliterative angiopathy (Oversohl, 1978).

2. Benditt and Benditt (1973) favour the notion that the cellular plaques were the result of a monoclonal cell-proliferation and that 75% of all plaques consist of "clearly monotypic" cells. Monoclonal myocytes might arise in the atheromas as a result of "wear and tear" during the intermitotic regeneration by indirect metaplasia and these cells maintain a certain independence similar

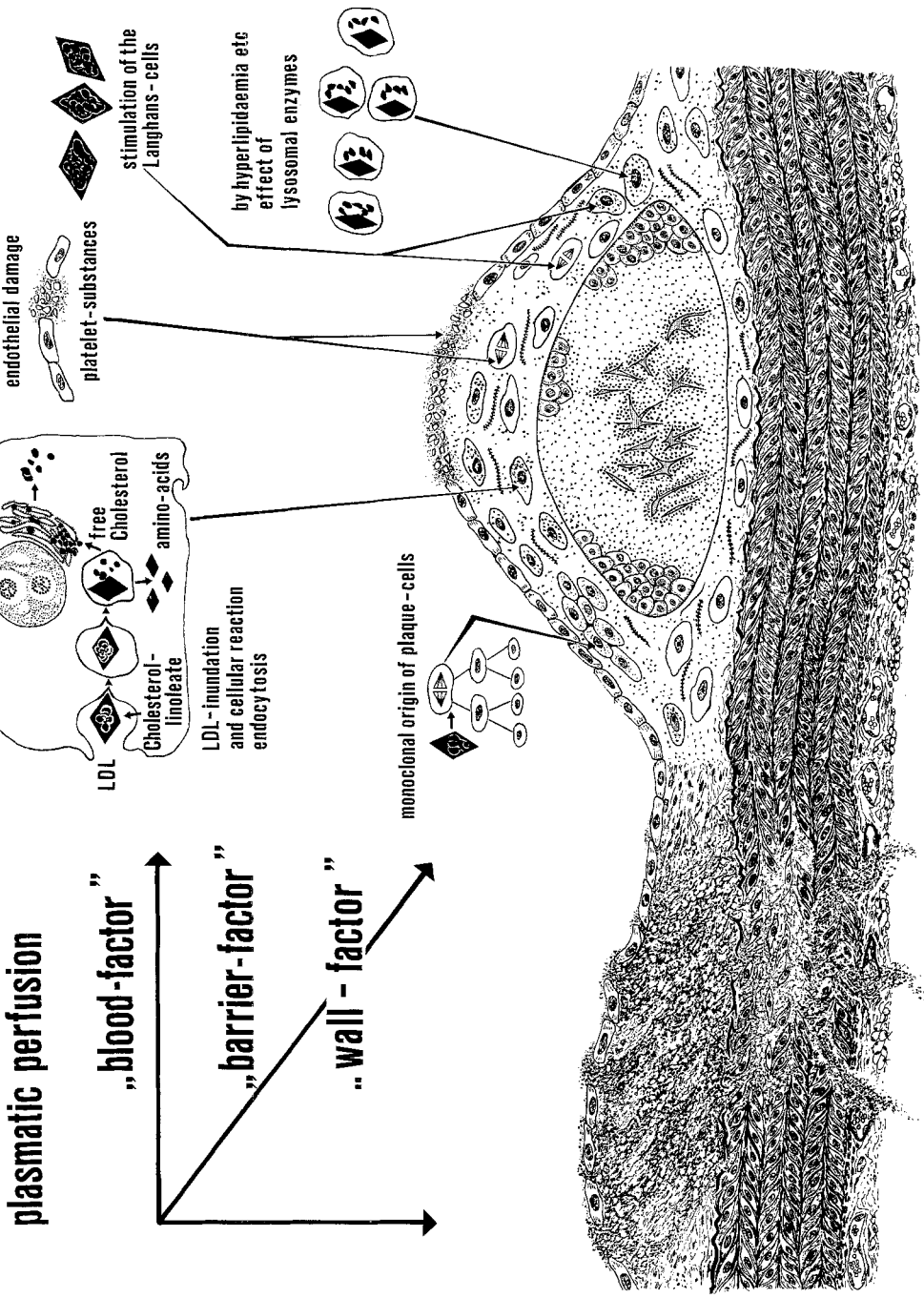

Fig. 8. Scheme of the formale pathogenesis of the arteriosclerosis. Left: events during impaired perfusion after Doerr (1970, p. 652) right: certain cellular proliferation, after Wissler (1977b, p. 215)

to that of benign tumours. These cellular tumours arose at predilective sites, and viral attacks, cigarette smoking, lipoprotein-actions or hormones might be factors in causation. These authors also point out that during smoking there is a formation of aryl-hydrocarbons which are mutagenic. Whether Baumgartner's platelet-material has a mutagenic effect is also discussed at present. Benditt's thesis has provided a strong stimulus and is worth detailed consideration.

We have been working on the cells of the vessel wall. In situ they show often a star-like shape, after culturing for several days they show marked grouth. After 8 days one sees (electron-microscopically) a formation of fibrils. By immunofluorescence-microscopy, contractile proteins can be demonstrated at this stage (Hofmann and Goger, 1977).

Hofmann and Darai hybridised smooth muscle-cells of human arteriosclerotic plaques and of Tupaia (Asian squirrel) with DNA-virus and obtained monoclonal tumour-like populations. The reimplantation in Tupaia is planned and we hope to induce an angiopathy similar to the human juvenile sclerosis.

There is no doubt about the continuous "covert" infiltration of blood plasma-components into the intima. Normally there is a constant relation between plasmaproteins in the circulating blood and those in the ground-substance of the intima (Smith, 1977). Smith (1977) showed that during ageing, lesions of the endothelium become more common and that the permeability of the inner surface of the arterial wall is increased in the elderley. The notion is in line with the "Leipzig school" (Krug, 1976; Fuchs, 1977). Giampalmo differentiated between a "private" and a "public" pathology of the arteries (1958, 1967) – the "private" structurally dependant one, and the "public" one related to the struggle between conducting pipes and their "freight". If Virchow's notion that pathology is physiology with obstacles is right then public struggle is the more important, and impairment of plasmatic perfusion is a basic phenomenon determining the fate of the arteries.

If we subsume the wide variety of arteriosclerotic lesions into two main pathogenetic types then it is clear that there are two patterns of events leading to the lesions – often in combination. With Bouissou I belive that arteriosclerosis is a generalized process which is more distinct where the elastic-muscular-junction is severely degenerated. In the case of severest disturbance the result is a dissecting scler-atheromatosis. I agree with Wissler and coworkers that arteriosclerosis is a polytopic, locally proliferative, cellular phenomenon. The first form (left side Fig. 8) occurs usually in the elastic, the second form (right side Fig. 8) usually in the muscular arteries. This separated view does not imply "either – or", because there are combinations of the two forms. Experimental atherosclerosis is also a generally mixed process (Chomette et al., 1977) and thus difficult to interpret.

The arteriosclerosis of Figure 8 (left side) is a matter of destiny (in German: "somatisches Fatum"), whereas the sclerosis of Figure 8 (right side) involves exogenic factors, it is acquired and might therefore be treatable.

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