Virchows Arch [Pathol Anat] (1983) 401:185–201

Virchows Archiv A

Manifestation and ultrastructural typing of amyloid deposits in the heart*

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Summary. Using light and electron microscopy, 65 cases of amyloid deposits in the heart were examined. Five different groups were distinguished: I. isolated atrial amyloidosis, II. senile cardiac amyloidosis, III. cardiac amyloid accompanying chronic infections and tumors, IV. cardiac amyloid accompanying plasma cell dyscrasia, V. idiopathic cardiac amyloidosis.

Seen structurally, no principal differences in the precise localization of the amyloid deposits were found in any of the groups investigated. Amyloid is always deposited in the vicinity of cells with myocytic cell differentiation (i.e. the heart muscle cells, non-striated muscle cells of the vessels), whereby the relevant basement membranes serve as conductors. A systematic relationship between amyloid and the collagenous fibers of the interstitium or the tunica adventitia of the vessels could not be demonstrated, which shows the concept "pericollagen" to be inadequate for the morphological characterization of amyloid deposits in the heart. Whereas for group I a localized mechanism for the production of amyloid must be considered, in the case of groups II–V a vascular principle expression of a generalized amyloidosis seems to be the major factor. The question of the differing concentration of amyloid deposits in the heart suggests that localized factors (e.g. changes in the myocytic basement membranes) and quantitative changes of the amyloid-building proteins may also be important.

Key words: Amyloidosis of the heart – Myocardial affection – Vascular (arterial) affection – Principles of deposition

A systematic observation of the forms of cardiac amyloidosis leads to the identification of two groups. Deposits may occur:

1. as part of a generalized amyloidosis (for example in amyloidosis associated with plasma cell dyscrasia and idiopathic amyloidosis) and

* Supported by Deutsche Forschungsgemeinschaft Schn 231/1

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2. in the form of a localized amyloidosis, apparently restricted to the heart as a manifestation of the so called senile amyloidosis (Soyka 1876). According to the location and extent of the cardiac amyloid involvement, the result is either an absence or varying degrees of functional disturbance of the heart, somtetimes leading to death (Jansen 1962; Baghirzade 1967; Chew et al. 1975; Hodkinson and Pomerance 1977).

Clinical manifestations depend on the amyloid deposits in the interstitial space, particularly in the myocardium. Different assertions about the relationship between amyloid and the different substructures of the interstitial space have been made. In the histological amyloid systematisation of Missmahl and Gafni (1964) cardiac amyloid is classed with the pericollagen forms of amyloidosis, which indicates a preferential relationship between the amyloid fibrils and the collagenous fibers. The purpose of this investigation is to analyse more closely and systematically, the exact localization of the amyloid deposits in the heart. Electronmicroscopy is used since previously only individual cases have been studied in this way. Our analysis will be attempted in the light of newer insights into the biochemically defined amyloid proteins, which make possible a new systematisation of the forms of amyloidosis in general (Glenner et al. 1980; Schneider and Thoenes 1982), and specifically of cardiac amyloid (Cornwell and Westermark 1980; Westermark et al. 1980).

Material

Using autopsy material from the Pathology Department of the University of Mainz from 1970–1982, 64 cases with amyloid deposits of the heart were examined (Table 1). The age of the patients was between 17 and 101 years, the relationship between male and female was approximately 1:1. In addition, a myocardial biopsy of a 43 year old patient was made available for examination (by the Department of Internal Medicine of the Justus Liebig University in Gießen, Prof. Dr. G. Schütterle).

Methods

Light microscopy. In the individual cases up to 14 autopsy specimens from the heart (right and left atrium, right and left ventricle) were examined. The conduction system, the cardiac valves and the extramural coronary arteries were not examined systematically. Fixation in buffered, 4% formaldehyde, was followed by preparation of ca. 5 µ thick paraffin sections, and staining with haematoxylin-eosin, van Gieson, silver staining according to Ehrenreich and Espinosa (1971), Congo red according to Puchtler et al. (1962); and the demonstration of amyloid presence using Congo red stained sections on the basis of green birefringence under polarized light.

Electron microscopy. Nine cases were chosen for electronmicroscopical investigation and an average of 4 tissue sections from the endocardium, the atrial and ventricular myocardium, the intramural arterial system and the epicardium were examined. Autopsy material was taken as 1 mm^3 sections of tissue, in part immediately after opening the non-fixed heart (4–24 h post mortem) and in part from a heart fixed in toto in 4% formaldehyde secondary fixation in 4% formaldehyde. The biopsy material was in 1 mm^3 fixed in a 3% buffered solution of glutaraldehyde, in each case secondary fixation in a 1% buffered solution of osmium tetroxide and embedding in epon, was carried out before preparation of semi-thin sections, staining with methylene blue and in some cases silver staining according to Movat (1961).

Ultra-thin sections were prepared with an ultramicrotome OM U2 (Reichert), with subsequent contrasting with uranyl acetate and with lead citrate, and in some cases silver staining of the ultra-thin sections according to Movat (1961). Electron microscopic photographs were taken with the Philips electron microscope EM 301.

Since the investigation reported on here was mainly based on autopsy material, only in a few cases was an optimal tissue fixation be achieved. This must be taken into account when considering the visual material from the electron microscope; this does not, however, affect the statements made concerning the localization of the amyloid fibrils.

Table 1. List of patients examined arranged into 5 groups according to Glenner (1980)

Autopsy number	Age	Sex	Basic disease	Heart weight (gram)	Macroscopic diagnosis
Isolated atrial amyloidosis (A-IAA) n=32:					
314/79	78	m	Diabetes mellitus	500	+
672/80	73	f	Hypertension	380	
687/80	79	f	Hypertension	550	
695/80	76	m	carcinoma of the urinary bladder	380	
708/80	78	m	carcinoma of the prostate	370	
715/80	74	f	myelomatosis	530	
734/80	72	f	Arterial sclerosis	380	
737/80	81	f	Arterial sclerosis	340	
742/80	73	f	carcinoma of the stomach	210	
743/80	82	f	Arterial sclerosis	340	+
748/80	71	f	carcinoma of the pancreas	270	
749/80	66	m	Arterial sclerosis	500	
763/80	71	f	carcinoma of the large intestine	220	
768/80	87	f	Hypertension	480	
769/80	79	m	carcinoma of the lung	390	
781/80	86	f	Hypertension	490	
787/80	71	f	Arterial sclerosis	380	
794/80	77	m	Hypertension	710	
801/80	75	f	Hypertension	500	
806/80	82	m	Hodgkins disease	420	
853/80	80	f	Diabetes mellitus	450	
23/81	79	f	carcinoma of the stomach	200	
65/81	77	f	Diabetes mellitus	350	
68/81	95	f	Arterial sclerosis	270	
75/81	75	f	Hypertension	600	
84/81	85	f	Hypertension	410	
88/81	86	f	Hypertension	360	
98/81	77	f	Lymphoma	360	
149/81	66	f	bronchial asthma	360	
175/81	76	m	Arterial sclerosis	250	
186/81	68	m	Hypertension	400	
202/81	70	f	Hypertension	330	
	∅ 77			∅ 400	
Senile cardiac amyloidosis (A-SCA) n=4:					
954/79	101	f	Arterial sclerosis	360	+
559/80	81	f	Arterial sclerosis	360	
797/80	98	f	Arterial sclerosis	320	+
18/81	75	f	Arterial sclerosis	350	
	∅ 89			∅ 350	

Table 1 (continued)

Autopsy number	Age	Sex	Basic disease	Heart weight (gram)	Macroscopic diagnosis
Cardiac amyloidosis accompanying chronic infections and tumors (A-A) n=11:					
1122/70	31	m	Bechterew's disease	410	
821/72	51	f	carcinoma of the breast	380	
596/73	59	f	Glioblastoma	270	
495/74	68	m	Osteomyelitis	480	
96/75	17	m	Hodgkin's disease	200	
473/76	61	m	Crohn's disease	240	
659/76	68	m	carcinoma of the kidney	360	
22/77	49	m	psoriatic arthritis	370	
171/80	65	f	Polyarthritis	440	
194/81	64	f	Tuberculosis	380	
427/81	54	f	carcinoma of the kidney	300	
	∅ 63			∅ 350	
Cardiac amyloidosis accompanying plasmacell dyscrasia (A-L) n=6:					
1117/72	61	m	plasmocytoma	430	
116/76	44	m	plasmocytoma	580	+
16/79	79	f	plasmocytoma	520	+
762/79	68	f	plasmocytoma	420	+
394/81	78	f	plasmocytoma	450	+
173/82	41	m	plasmocytoma	480	+
	∅ 62			∅ 480	
Idiopathic cardiac amyloidosis (A-A or A-L) n=11:					
180/73	60	m		350	
206/73	63	m		600	+
412/73	59	m		750	
255/75	58	f		370	
928/76	64	m		460	+
14/77	71	m		470	
581/77	64	f		300	
5736/78B	43	m		–	
244/79	74	f		725	+
355/79	56	m		410	+
782/79	77	f		300	
	∅ 63			∅ 475	

Results

Since the emphasis of our investigation is on the histological manifestation of amyloid deposits in the heart, we will begin by describing the topography of the amyloid deposits according to the customary layers (endocardium, myocardium, epicardium), irrespective of the individual cases. Then their relationship to the biochemically defined amyloid groups will then be established.

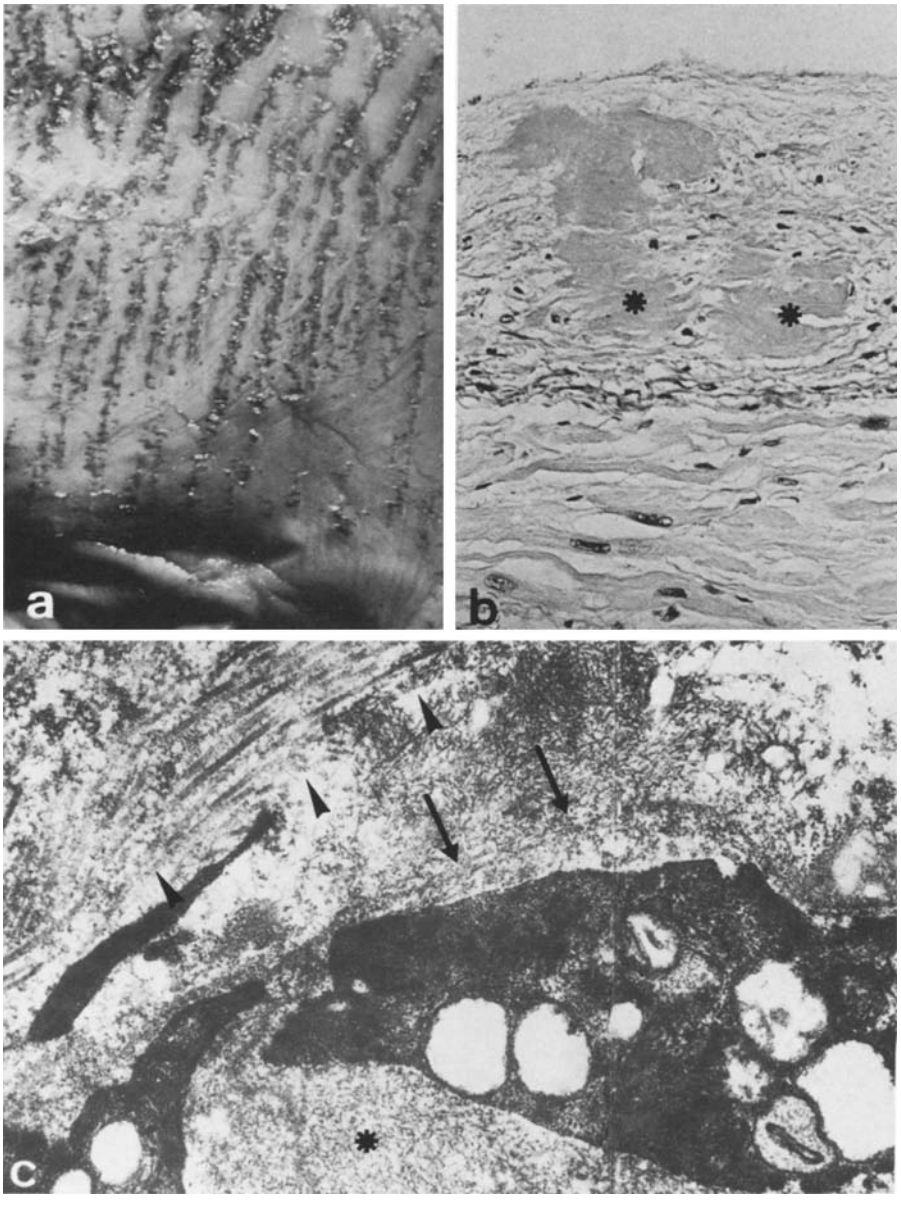

Fig. 1. **a** Atrial endocardium with amyloid deposits (macro). ×4. **b** Atrial endocardium with plaquelike amyloid deposits (*), (Congored). ×320. **c** Atrial endocardium with amyloid deposits (*) around non striated muscle cells. Myocytic basementmembrane (↑), collagen fibers (▲). ×25,000

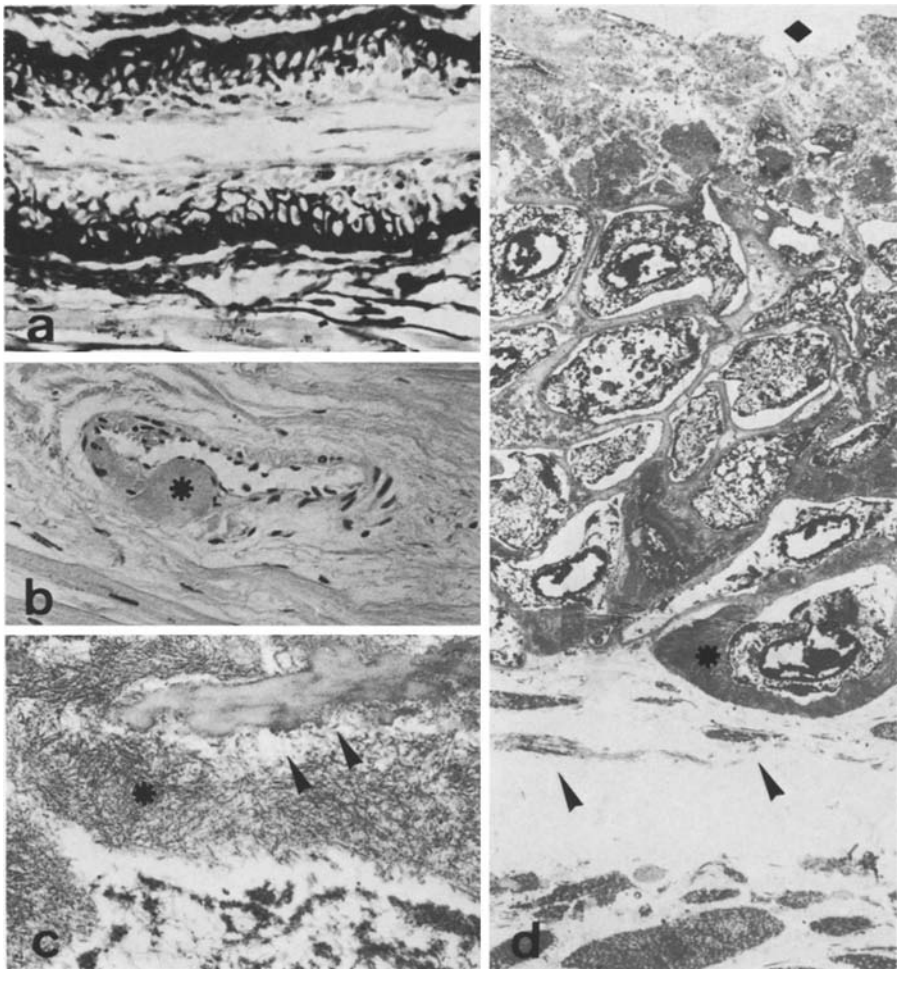

Fig. 2. **a** Myocardial artery with amyloid infiltration of the outer part of the tunica media, staining according to Ehreneich and Espinosa. × 240. **b** Small artery with a plaquelike amyloid deposit (*), Congored. × 240. **c** Inner part of the tunica media with amyloid fibrils (*) and splintered lamina elastica interna (▲). × 25,000. **d** Myocardial artery with amyloid infiltration (*), amyloid free collagen fibers in the tunica adventitia (▲). × 3000

1. The topography of amyloid in the layers of the heart based on light and electron microscopic findings

Endocardium (Fig. 1 a–c). Under the light microscope the mostly plaque-like amyloid deposits are always found in the subendothelial stratum and are more pronounced in the myoelastical stratum with its numerous muscle cells (Fig. 1 b).

Under the light microscope band-like pulvinate, less frequently penicillate, amyloid depots are recognizable closely related to non-striated muscle cells of the endocardium. In this way, as shown electronmicroscopically

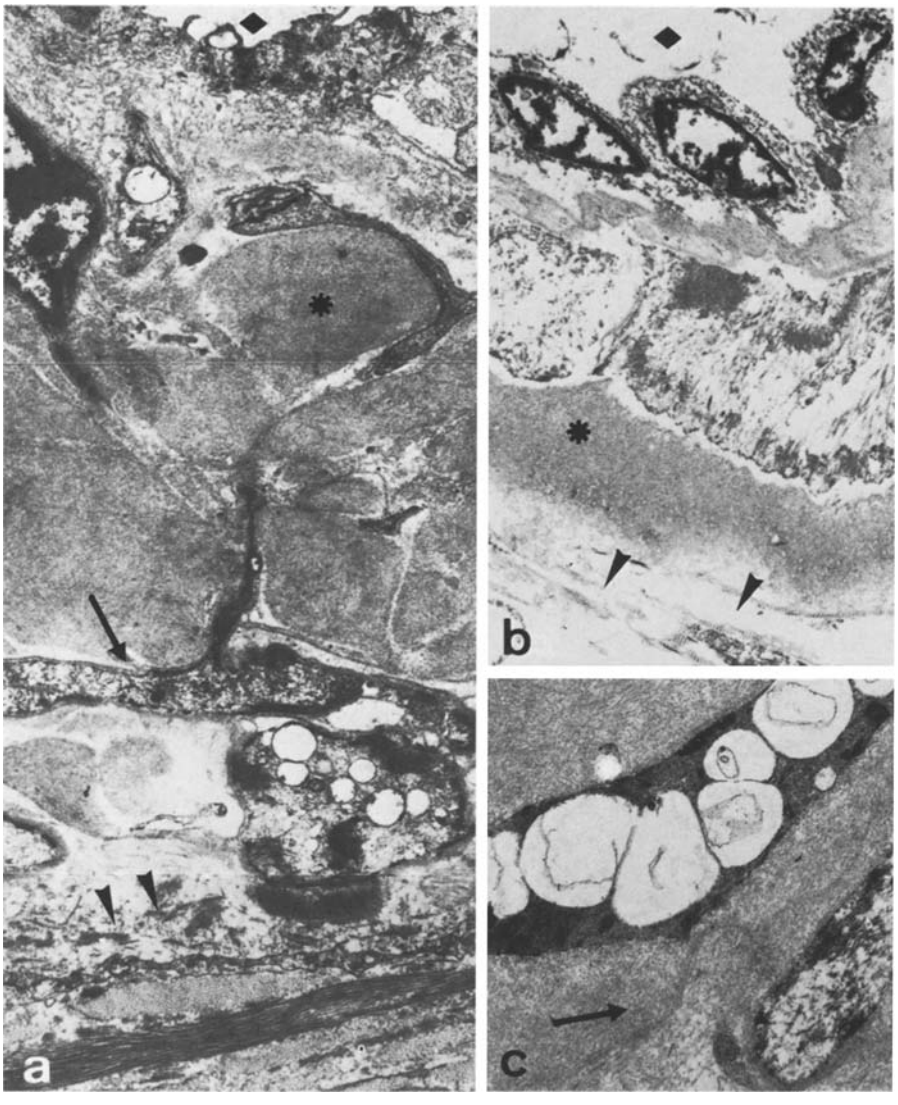

Fig. 3. a Small myocardial artery with amyloid infiltration, amyloid fibrils laid on the basement-membrane (↑) of muscle cells, amyloid free collagen fibers in the tunica adventitia (▲). × 7000. **b** Arteriole with amyloid deposits (*) around the outer part of cells of the tunica media, amyloid free collagen fibers in the tunica adventitia (▲). × 5,900. **c** Strong amyloid infiltration of tunica media with degeneration of muscle cells, amyloid fibrils with disappearing basement-membrane (↑). × 9,900

the fibrillar amyloid substance is deposited on the outside of the myocytic basement membrane or intermingled with it, resulting in its disappearance (Fig. 1 c). The regions of densely packed collagen fibers, between the muscle cells, are chiefly free of amyloid. Only at their edges and uncommonly at their centers can small, discontinous amyloid deposits be found, which are randomly scattered between the collagen fibers (Fig. 1 c).

Myocardium. Under the light microscope two preferred localizations are of primary importance and these cannot always be dissociated:

a) the intramural vascular system (Figs. 2–4),

b) the area around the cardiac muscle cells (Figs. 5, 6).

a) The intramural arteries (small arteries and arterioles) exhibit amyloid deposits primarily in the tunica media. Generally speaking, there is an increase in the amyloid deposits from inner to the outer media section (Fig. 2a). Occasionally a complete and uniform occupation of the tunica media by amyloid is seen (Fig. 2d, 3a). Focal, pulvinate amyloid depots are seldom observed (Fig. 2b). When non-striated muscle cells are completely surrounded by amyloid they show signs of atrophy (Fig. 3c). In addition, electron microscopic examination shows that the basement membranes associated with the muscle cells have merged to a large extent with the amyloid mass (Fig. 2c, 3a). Intimal amyloid deposits in the form of subendothelial amyloid pads are seldom observed. Amyloid deposits in the tunica media terminate with a covering around its extreme outer muscle cell layer in the direction of the tunica adventitia; i.e., the tunica adventitia, containing collagen, is normally free of amyloid (Fig. 2d, 3a). Only small isolated offshoots of the amyloid deposits associated with the tunica media which reach into the adventitial connective tissue can be identified. We never found a systematic amyloid invasion of the tunica adventitia.

When interstitial capillaries of the myocardium have been altered by amyloidosis (for instance due to AL-amyloidosis, see below), they are in most cases completely surrounded by amyloid (Fig. 4a), which is always found on the endothelial and pericytic basement membranes (Fig. 4b). Venules and veins can also exhibit perimyocellular amyloid deposits of the tunica media, this, however, was only occasionally observed.

b) In the vicinity of the cardiac muscle cells focal or diffuse deposits can be identified with the help of the light microscope or, when necessary, the electron microscope:

In the case of focal deposits (Fig. 5a) groups of muscle cells together with capillaries within a histological section are partly or totally enveloped by amyloid (Fig. 5c), whereby hypertrophied cardiac muscle cells on the edges and atrophied cardiac muscle cells in the middle can be observed. Often clearly defined, large amyloid plaques develop.

In diffuse deposition (Fig. 5b), a reticular permeation of the myocardium in the section was seen, with regular bands of amyloid completely encasing the cardiac muscle cells.

Under the electron microscope similar ultrastructural characteristics can be seen: The amyloid fibrils attach themselves in the form of bands of differing width to the basement membranes of the cardiac muscle cells (Fig. 6b); they follow the undulating cell contours and also extend into deep sinuses (Fig. 6a). In cases of extreme amyloid invasion the myocytic basement membranes are no longer indentifiable, so that the amyloid fibrils are directly adjacent to the muscle cell membrane. Intracytoplasmic amyloid fibrils were never found. The collagen fibers are located in the amyloid-free interstitial space and are only secondarily involved in the amyloid pad

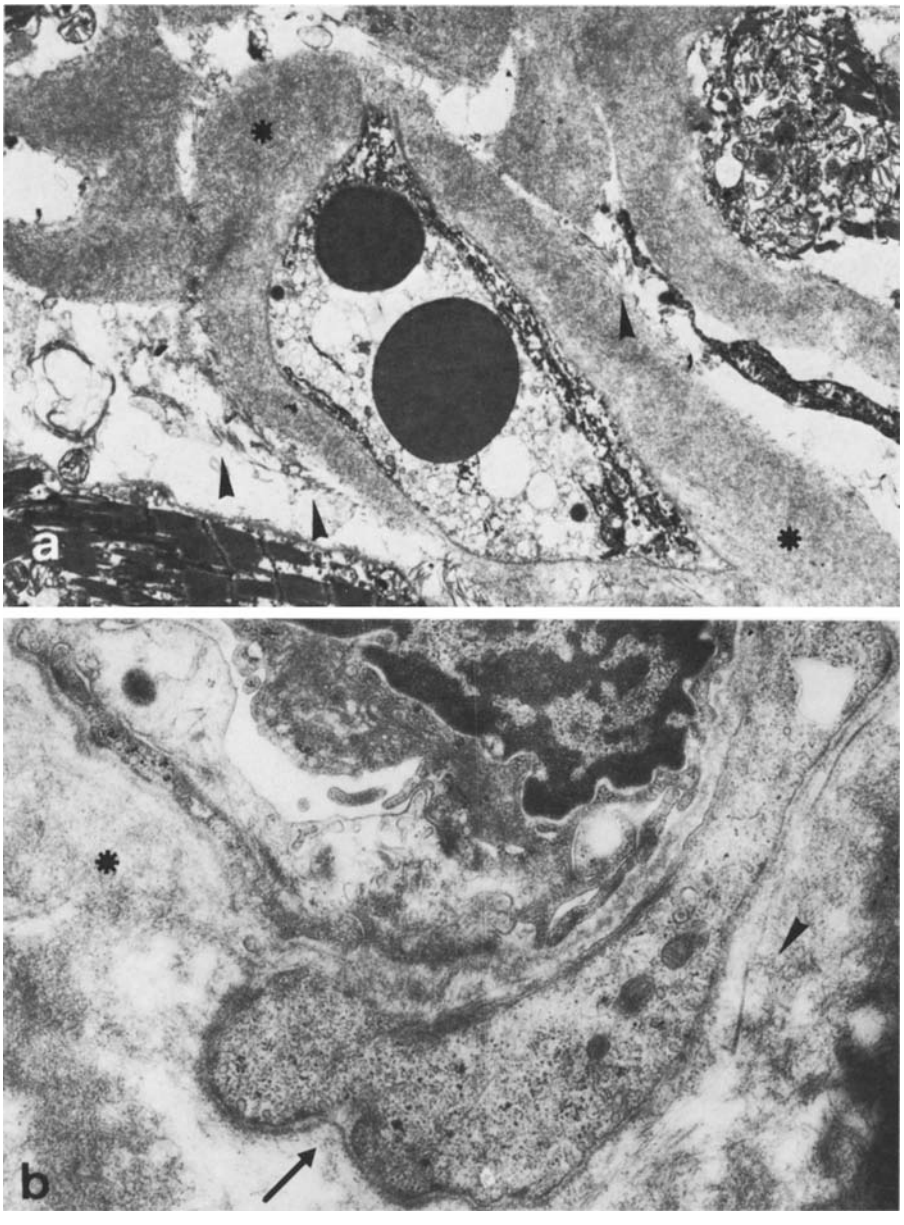

Fig. 4. **a** Myocard interstice with amyloid infiltration of a capillary wall (*), amyloid free collagen fibers (▲). × 4,400. **b** Part of a capillary wall with amyloid fibrils (*) orientated on basement membranes (↑), woven in collagen fibers (▲). × 20,000

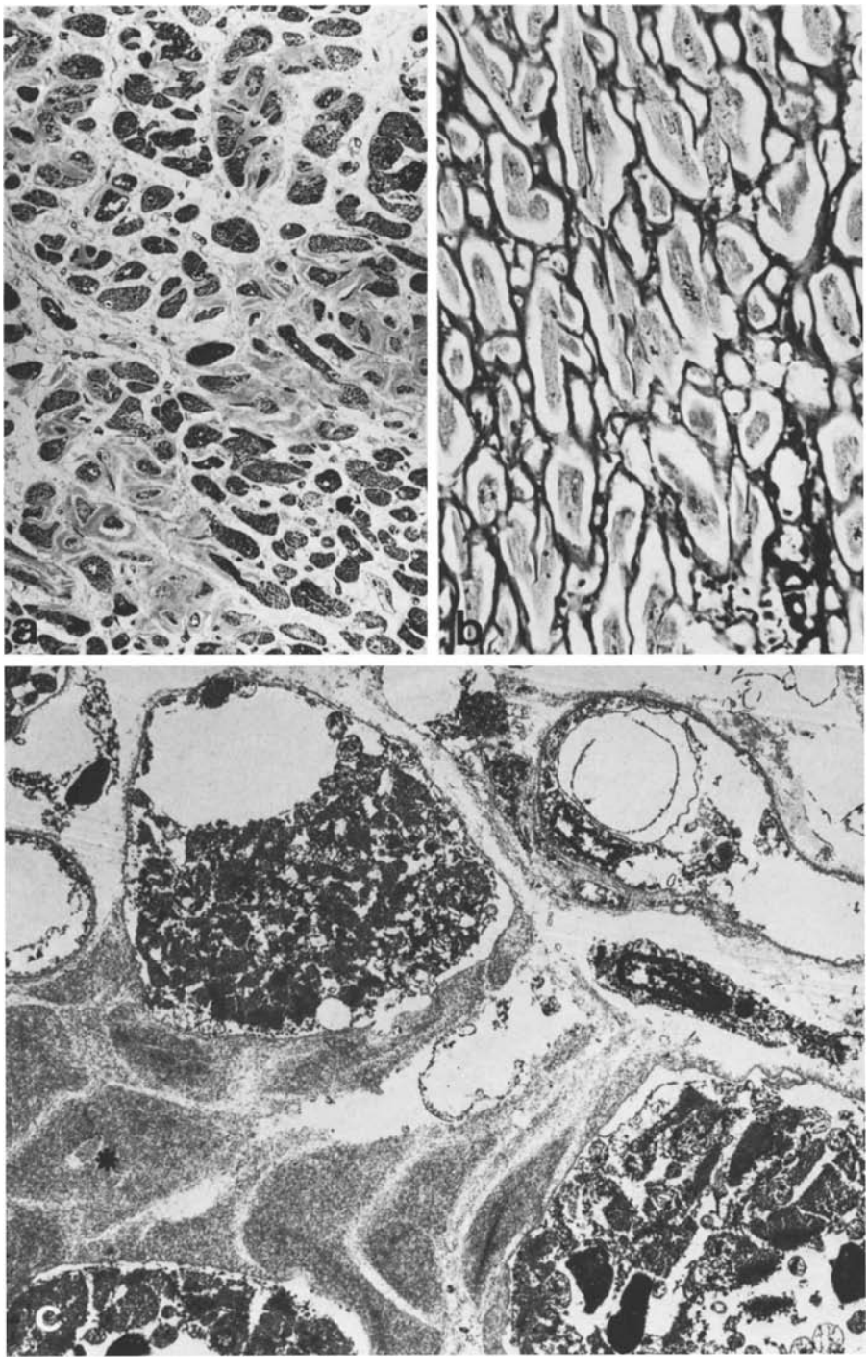

Fig. 5. **a** Myocardium with focal amyloid infiltration, methylenblue. × 240. **b** Myocardium with diffuse amyloid infiltration, staining according to Ehrenreich and Espinosa. × 320. **c** Focal amyloid infiltration (*) with segmental involvement of the outer sarcolemma of cardiac muscle cells. × 4,400

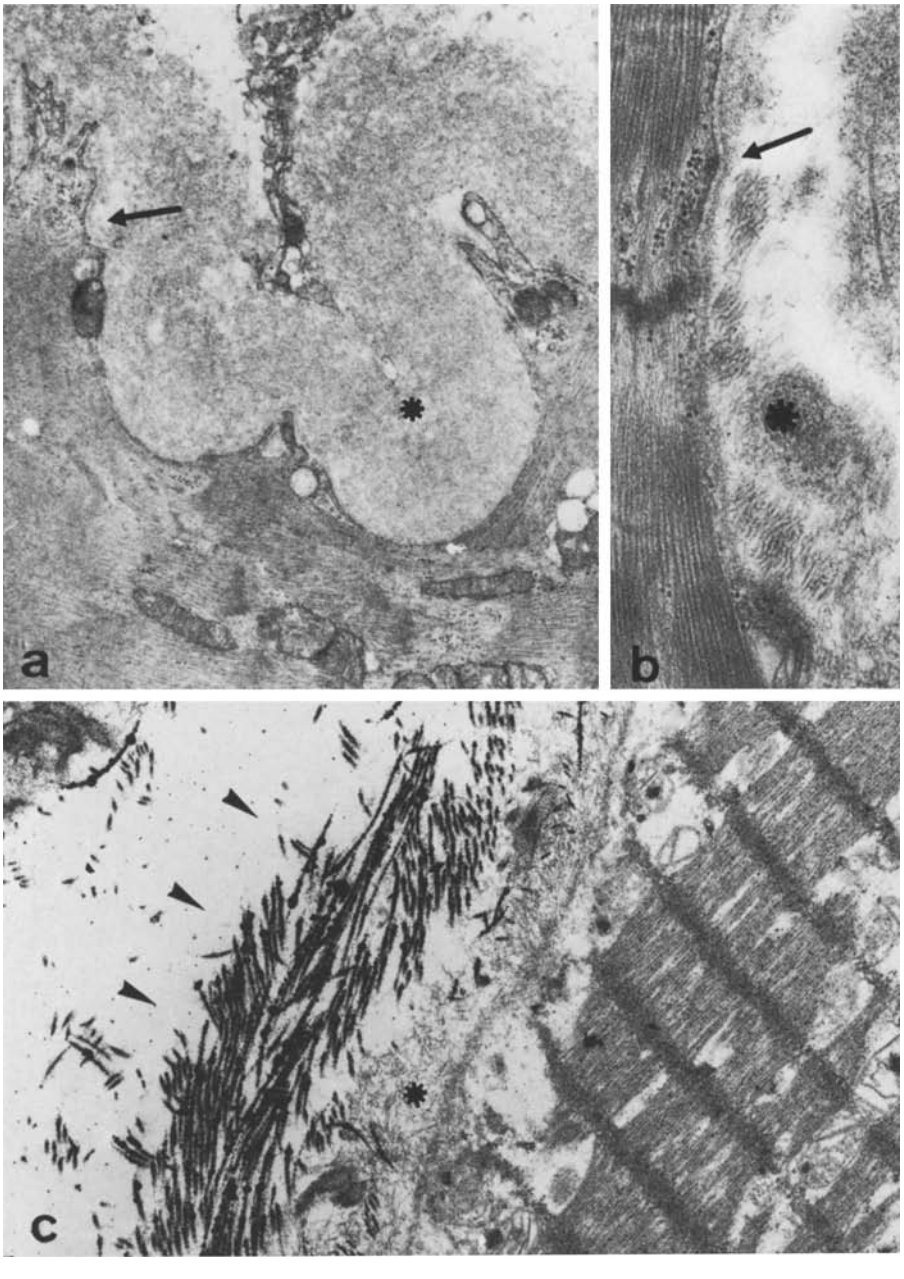

Fig. 6. **a** Amyloid fibrils (*) in the invagination of cardiac muscle cells, basement membrane (↑). ×1,600. **b** Amyloid fibrils (*) orientated on the basement membrane (↑) of cardiac muscle cells early stage of amyloid infiltration. ×37,500. **c** Amyloid fibrils (*) between a cardiac muscle cell and Movat stained interstitial collagen fibers (▲). ×13,100

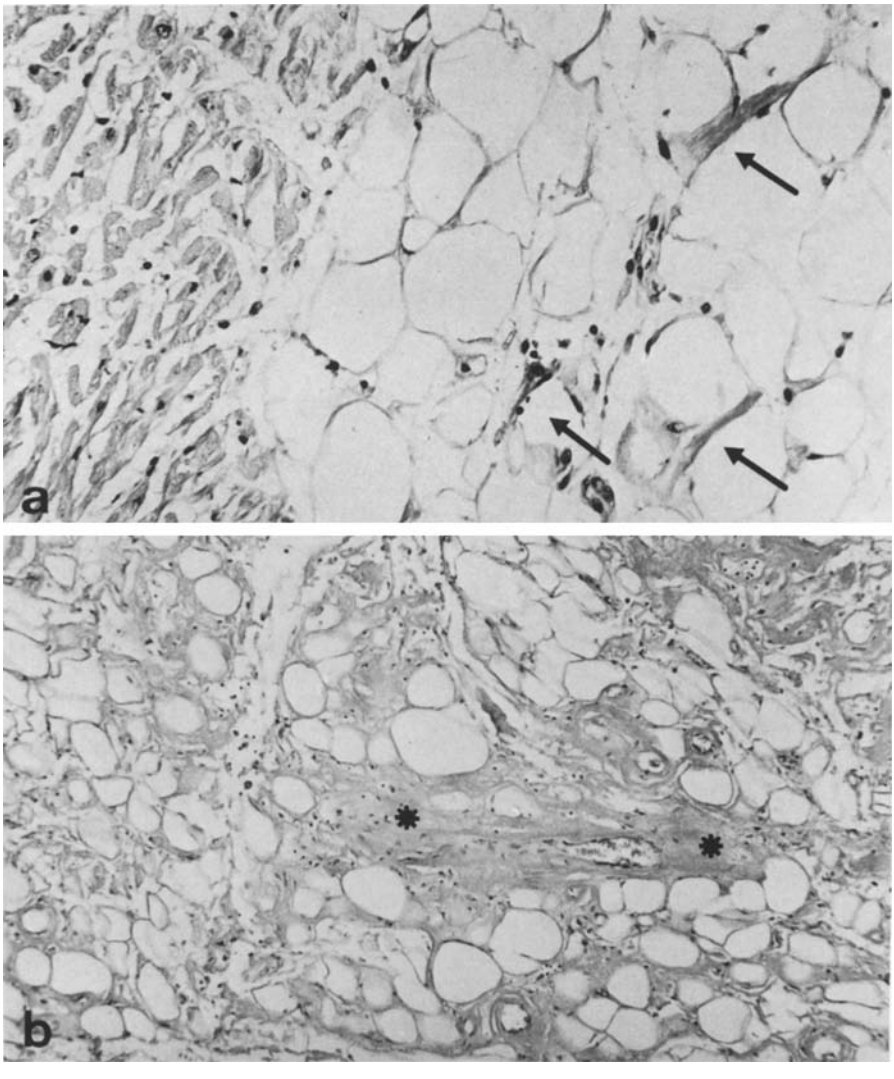

Fig. 7. a Epicardium with small amyloid deposits (↑) in the interstice of the fatty tissue, Congored. ×240. **b** Epicardium with heavy amyloid infiltration forming amyloid plaques (*) and nets, Congored. ×160

(Fig. 4a, 6c). A systematic relationship between the collagen fibers and the amyloid fibrils could not be demonstrated.

Epicardium. In the epicardial fatty tissue only isolated small amyloid centers are present. They are ordinarily found in the vicinity of the numerous capillaries and arterioles present in the fatty tissue and are conspicuous as narrow bands of amyloid associated with the vessels (Fig. 7a). Occasionally, in extreme cases, larger amyloid networks and plaques occur, so that individual fat cells or groups of fat cells seem to be totally encased in amyloid (Fig. 7b).

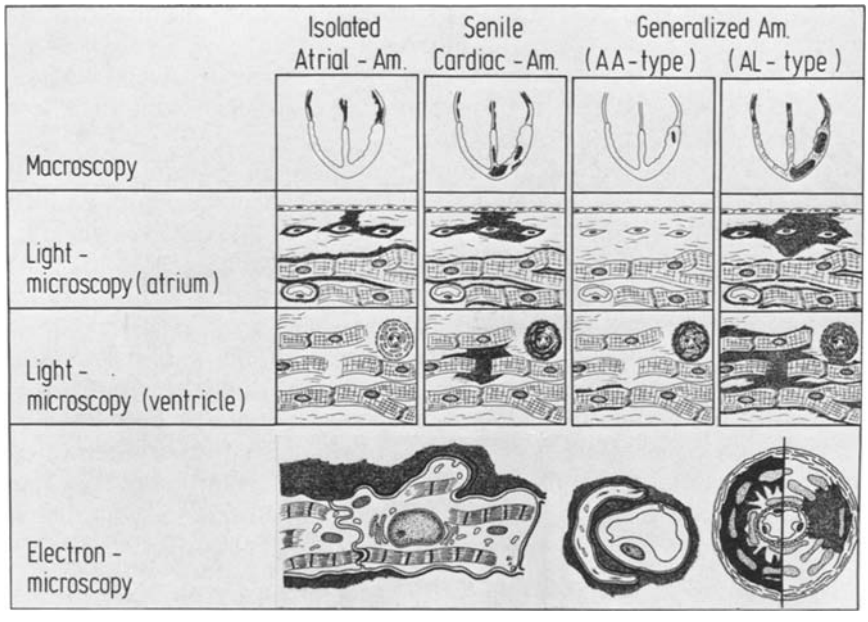

Fig. 8. Schema of the amyloid deposition in the heart arranged into 4 (5) groups according to Glenner (1980) and the macroscopical (*upper row*), light (*middle rows*) and electronmicroscopical (*bottom row*) appearance of the amyloid infiltration

2. The relationship between the localization of amyloid and pathoanatomically/pathogenetically defined forms of cardiac amyloidosis

What is the relationship between the localization of amyloid described above and the various forms of cardiac amyloidosis? In connection with the protein-chemically orientated amyloid classification of Glenner (1980; additional literature in Schneider and Thoenes 1982) the following groups can be identified in general and, as a result, also apply to the cases examined by us:

I. Isolated atrial amyloidosis
(type A-IAA) $n=32$

II. Senile cardiac amyloidosis
(type A-SCA) $n=4$

III. Cardiac amyloidosis in cases of chronic inflammatory diseases and tumors
(type A-A) $n=11$

IV. Cardiac amyloidosis in cases of plasma cell dyscrasia
(type A-L) $n=6$

V. Idiopathic cardiac amyloidosis
(type A-A/A-L) $n=11$

Figure 8 will give a short description of the macroscopic and microscopic characteristics of the above listed groups with amyloid involvement of the heart presented in their most common form (Idiopathic cardiac amyloidosis is excluded, because the histologic appearance does not differ from the amyloidosis of the A-A type or the A-L type).

Differences can be seen in the topography on the macroscopic level (top row), which shows a lack of amyloid deposits in the ventricle wall in cases of isolated atrial amyloidosis and in the atria in cases of a generalized amyloidosis of the A-A type. On the histological-cellular level (middle rows) one recognizes a concentration gradient of the amyloid deposits ranging from pronounced vascular deposits in cases of generalized amyloidosis of the A-A type to a severe amyloid infiltration of the vascular system and the myocardium in cases of generalized amyloidosis of the A-L type. Independent of the pattern of the deposit the electron microscopic findings show a common principle (bottom row). Amyloid is primarily deposited in and on the basement membranes which preponderantly show a close relationship to cells with myocytic differentiation, in addition the endothelial basement membranes found in the vascular system are also affected.

Discussion

1. The topography of the amyloid deposits and their relationship to collagen

The analysis of amyloid deposits in the heart showed no essential differences in the exact localization of the amyloid deposits. On the light microscopical level, a constant, close relationship between the Congo red amyloid substance and the cardiac muscle cells of the atria and ventricles and the nonstriated muscle cells of the endocardium, the nonstriated muscle cells of the tunica media of small arteries and arterioles and the capillaries containing pericytes was evident. This suggests that the site of amyloid deposits in the heart is preponderantly cells with myocytic differentation, which was already discussed by Hüsselmann (1955).

Electron microscopic analysis makes it possible, to assign the amyloid substance to substructures. It can be seen that in all our cases the basement membranes serve as a conducting structure for the deposit of amyloid fibrils (Schneider 1980; Schneider and Thoenes 1982) whereby prevailingly myocytic basement membranes are affected and beyond this the endothelial basement membranes of the vascular system are concerned. In cases with light amyloid deposition the basement membranes can still be clearly identified within the amyloid masses and in more extreme cases they are only fragmentarily present or may be missing completely. Similar observations were reported by Schroeder et al. (1975) and Chan and Ikram (1977). The close relationship of amyloid to the basement membranes is, according to Schroeder et al. (1975), also documented by the presence of amyloid fibrils in the myocytic cell invagination. In contrast to the findings of Husband and Lannigan (1968) and Hedner et al. (1975), the cytoplasmic membrane in our material always remained intact.

In cases of light amyloid invasion of the myocardium, independent of the protein type of amyloidosis, our findings were similar to those of Hedner et al. (1975); the interstitial space between the myocytic or between the myocytic and vascular amyloid band was free of amyloid, whereby the collagen fibers were not systematically included in the amyloid deposits. We only observed inclusion of the collagen fibers in very narrow interstitial spaces and/or accompanying an extensive permeation of the tissue with amyloid.

As mentioned at the outset, cardiac amyloidosis is classified as a "pericollagen" form of amyloidosis, which would indicate a preferential relationship between the amyloid fibrils and the collagen fibers. Our findings show, in contrast to this, that the collagen fibers located in the interstitium between the muscle cells do not play an essential role in connection with the deposit of amyloid. The next step which suggested itself was to examine this question in connection with the arterial wall, since if a pericollagen type of deposit were present one would expect the deposits to be concentrated on the tunica adventitia, which is rich in collagen fibers. Our findings show, however, a preferred amyloid involvement of the collagen fiber-free tunica media of the arteries, one which progresses in the initial stages from the outer tunica media toward the middle (centripetally). In the process the outer muscle cell layer becomes completely enclosed by amyloid and finger-shaped amyloid offshoots branch out into the inner media sections. In most cases we did not, however, find an involvement of the tunica adventitia – except in far advanced cases with an extensive deposit of amyloid which then simultaneously involves the tunica media. As a result of our electron microscopical investigations of cardiac amyloidosis, the concept "pericollagen" for the morphological characterization of the amyloid deposits in the heart no longer seems suitable. A relationship of amyloid to the collagen fibers seems to be simulated by the close vicinity of the amyloid-binding basement membranes (Schneider and Thoenes 1982) to the collagen fibers of the interstice.

2. Amyloid localization and the forms of cardiac amyloidosis

Apart from the principles of deposition which are common to all forms of amyloidosis of the heart, the interesting question remains: what is the cause of the topographical differences which are characteristic of the five pathoanatomically defined groups of cardiac amyloidosis? Jansen (1962) has made some suggestions in this area. A fundamental difference seems to exist between isolated atrial amyloidosis, which is a purely local form limited to the atria (group I) and the remaining forms of cardiac amylodosis (groups II–V), which have the following characteristics in common: involvement of several heart regions, involvement of the intramural arterial system and a variable involvement of the area around the cardiac muscle cells. The localized character of isolated atrial amyloidosis, which is analogous to numerous localized forms of amyloidosis may indicate that a in loco released amyloid building protein is at work here (Westermark et al. 1979;

Looi 1981). It must, however, be mentioned, that in cases of (A-L) cardiac amyloidosis, which are caused by plasma cell dyscrasia and therefore definitely of systemic origin, the same kind of atrial involvement can be observed to that seen in isolated atrial amyloidosis. Only after a chemical analysis of the fibrillar material in cases of atrial amyloidosis can this matter be clarified.

In the remaining groups of cardiac amyloidosis (II–V) the common characteristic among those mentioned above, which seems currently to be of particular importance is the amyloidosis of the intramural vessels, since it draws attention to a circulatory origin. This can certainly be considered valid for groups

III (cardiac amyloidosis in cases of chronic inflammatory diseases and tumors, type A-A);

IV (plasma cell dyscrasia-associated amyloidosis, type A-L) and

V (idiopathic amyloidosis, type A-A and A-L) (Glenner 1980).

It follows that the presence of amyloid in the heart in groups III–V is an expression of a generalized amyloidosis. In case of senile cardiac amyloidosis the same principle can be seen since Sletten et al. (1980) identified "pre-albumin" as the probable amyloid-building protein. It could also reach the heart by way of the blood stream and at the same time be transported to other organs, which could explain the findings of Berg (1968), Pomerance and Davies (1975) and Hodkinson and Pomerance (1977).

With these findings as a basis, the following question becomes critical: when in all these cases a general principle is responsible, what causes the varying intensity of the amyloid deposits around the cardiac muscle cells from group to group, sometimes also within a group, that is, what is responsible for that process which is the deciding factor for heart function (for instance for contractility)? It can be surmised that in this connection the supply route as well as the local concentration of the amyloid-building protein, together with a consideration of the time factor, play an essential role. This complex mirrors, then, the influence of the basic disease with its various processes, something which can be seen particularly clearly in cases of plasma cell dyscrasia combined with extreme myocardial amyloidosis. Further investigation is necessary to find answers to these questions and to find ways to prevent the functionally serious myocardial amyloidosis.

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Accepted July 7, 1983