Amyloidosis
From starch to molecular pathology

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Amyloidosis represents a group of diseases with the common feature of extracellular deposition of insoluble pathologic proteinaceous substance – **amyloid** – within the tissues (1,14). Amyloid stains pink with haematoxylin and eosin, its deposits appear amorphous under the light microscope. Stained with Congo red, amyloid displays an apple-green birefringence under the polarized light (1). By electron microscopy, amyloid is composed of non-branching linear fibrils, 7.5 – 10 nm in width and of indefinite length. Proteins of different origin and nature can form amyloid deposits. The prerequisite is the ability of these proteins to form cross-ß-pleated sheet conformation responsible for the distinctive staining and birefringence with Congo red (1). Apart from amyloid fibrils, other minor constituents, like serum amyloid P component, proteoglycans, and highly sulphated glycosaminoglycans are always present in amyloid deposits (9,14). The question how amyloid deposition within the tissue mediates the damage to its normal function has not been fully explained. Progressive extracellular accumulation of amyloid produces atrophy of adjacent cells. Moreover, interference with blood supply and blockage of transport between capillaries and cells also play a significant role in tissue and organ derangement (6).

The first descriptions of amyloid deposition in the organs originate from the 17th century. This period is known not only for the Thirty years war, but also for the introduction and widespread utilization of post-mortem examinations in human medicine. Amyloid deposition was observed macroscopically, either as homogenous "stony" foci in the spleen, or as homogenous hardening of organs. More detailed descriptions of amyloidosis originate from 19th century, when thousands of autopsies were performed by specialized physicians – pathologists. At this time, the term "lardaceous change" was used to describe macroscopic appearance of organs infiltrated with amyloid (4). Detailed description of organ involvement in amyloidosis originates from Carl Rokitanski, the famous pathologist of the 19th century, born in Hradec Králové. Rokitanski stated that greyish, lardaceous-gelatinous infiltration of organs appeared in patients suffering from chronic inflammatory diseases, like tuberculosis or syphilis. The term "amyloid", originally used in botany to describe a normal amylaceous constituent of plants, was introduced by another of the most significant pathologists of the 19th century, Rudolf Virchow. He described the peculiar reaction of slices from organs showing "lardaceous change" with iodine, resembling the staining properties of starch. Virchow also described amyloid involvement of the organs of the digestive tract, and pointed out the relation of marasmus with advanced amyloid disease. The proteinaceous nature of amyloid deposits was discovered by Carl Friedreich and August Kekule in the middle of the 19th century. This discovery provoked the discussion as to whether the term "amyloidosis" should be used. Finally, amyloidosis prevailed, probably due to the common use of the iodine stain and to Virchow's personality. Primary amyloidosis, not related to any chronic inflammatory disorder, was also described in the 19th century (12). Extension of light microscopy in pathology and new staining techniques enabled further detailed description of amyloid deposition within the tissues and significantly improved the diagnosis of amyloidosis. Metachromatic staining with methyl violet enabled doctors to clarify the extracellular nature of amyloid deposits. In 1922, Benhold introduced Congo red staining that helped to distinguish amyloid deposits from other non-amyloid hyaline substances (12). The history of this dye reflects not only the developments in the chemical industry in the 19th century, but also geopolitical events of this period. Congo red is an aniline dye created by the German chemist Paul Böttiger in 1883. He had sold the patent to the Aktiengesellschaft für Anilinfarbenfabrication (AGFA) Company, which started to produce it for staining textiles. The question why the dye was called Congo red remains a mystery. Circumstantial evidence points to the rela-

tion of this term to the major diplomatic West Africa Conference held in Berlin in 1884 – 1885. Since the central issue of the conference was Congo and this word was on the tip of every tongue, it should not be surprising that AGFA used this name as an effective marketing tool. It is clear that Congo red does not originate from this Western African country and, moreover, traditional native textiles from the Congo River basin are typically black and only rarely red (20).

Remarkable methodological developments in pathology and extension of biochemical approaches and methods of molecular biology during the 20th century enabled further progress in knowledge on the nature of amyloid. Distinct types of amyloid were characterized and basic pathogenetic mechanisms involved in formation of amyloid deposits were recognized. Recent classification, based on the mode of distribution of amyloid deposits, distinguishes two categories – systemic (generalized) amyloidosis and localized (isolated) organ amyloidosis. Systemic amyloidosis can be subclassified on clinical grounds into "primary" amyloidosis, associated with some imunocyte dyscrasia and "secondary" amyloidosis occurring as a complication of chronic inflammatory or tissue destructive processes (1). Clinical features of amyloidosis can be rather variable and its recognition quite uneasy as demonstrated by Kohoutová et al. (11) and by Pintér et al. (16) in this issue of the Journal.

Another widely extended classification of amyloidosis based on the identification of class of particular amyloid fibril protein distinguishes categories such as AL, AA, ATTR and others (9). About 23 unrelated biochemically distinct proteins are known to form amyloid fibrils in vivo (15). The most common are: **(1)** The AL protein made up of immunoglobulin light chains or their fragments produced by an abnormal clone of B lymphoid cells. B-cell dyscrasia, multiple myeloma or other immunoglobulin-producing B cell neoplasm producing incomplete immunoglobulin molecules are the cause of systemic AL amyloidosis (13,18). **(2)** The AA protein derived from a larger precursor, SAA (serum amyloid-associated) protein synthesized by the liver. Increased production of SAA leading to reactive systemic AA amyloidosis is related to chronic inflammatory conditions, like tuberculosis, bronchiectasis, rheumatoid arthritis and osteomyelitis (1,7,17). **(3)** Transthyretin (TTR), prealbumin, a normal serum protein that binds and transports thyroxin and retinol. Structurally normal TTR forms amyloid deposits in the heart of aged individuals suffering from senile systemic amyloidosis (22). A mutant form of TTR is deposited in genetically determined familial amyloid polyneuropathies and also in cardiac amyloidosis (8,10). **(4)** Beta$_2$ microglobulin (ß$_2$MG), ubiquitous cell surface protein associated with the MHC class I molecules. Increased serum level of ß$_2$MG leading to amyloid deposition predominantly in synovial membrane, cartilage and bone tissues, appears in patients on long-term haemodialysis (1,19). **(5)** ß-amyloid (Aß) protein, derived from the larger amyloid precursor protein (APP), expressed on the cell surface. Aß and its aggregates are neurotoxic (21), Aß amyloid is deposited within the nervous tissue in Alzheimer disease (2). **(6)** Prion (proteinaceous infective particles) proteins form amyloid deposits in transmissible spongiform encephalopathies, like Creutzfeldt-Jakob disease and in prion protein cerebral amyloid angiopathy (3,5). **(7)** Endocrine amyloid is derived either from polypeptide hormones or from unique proteins expressed by endocrine cells. Calcitonin-based amyloid is present in the stroma of medullary carcinoma of the thyroid gland, amyloid derived from atrial natriuretic peptide accumulates within the wall of heart atria of elderly patients (1). Amyloid based on the islet amyloid polypeptide deposited in the pancreas is strongly associated with the pathogenesis of type II diabetes (23).

Serial studies have shown that amyloid deposits are not inert and that they can be degraded (6,17). Possible treatment of amyloidosis is based on reduction of the respective fibril precursor protein and prevention of further amyloid deposition (6,18). This should enable regression of existing deposits with consequent improvement of organ function. New approaches to inhibit formation of amyloid fibrils and promote regression of amyloid deposits are being pursued.

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