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Review:

Protein folding pathology in domestic animals*

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Abstract: Fibrillar proteins form structural elements of cells and the extracellular matrix. Pathological lesions of fibrillar microanatomical structures, or secondary fibrillar changes in globular proteins are well known. A special group concerns histologically amorphous deposits, amyloid. The major characteristics of amyloid are: apple green birefringence after Congo red staining of histological sections, and non-branching 7–10 nm thick fibrils on electron microscopy revealing a high content of cross beta pleated sheets. About 25 different types of amyloid have been characterised. In animals, AA-amyloid is the most frequent type. Other types of amyloid in animals represent: AIAPP (in cats), AApoAI, AApoAII, localised AL-amyloid, amyloid in odontogenic or mammary tumors and amyloid in the brain. In old dogs Aβ and in sheep $APrP^{sc}$-amyloid can be encountered. AA-amyloidosis is a systemic disorder with a precursor in blood, acute phase serum amyloid A (SAA). In chronic inflammatory processes AA-amyloid can be deposited. A rapid crystallization of SAA to amyloid fibrils on small beta-sheeted fragments, the 'amyloid enhancing factor' (AEF), is known and the AEF has been shown to penetrate the enteric barrier. Amyloid fibrils can aggregate from various precursor proteins in vitro in particular at acidic pH and when proteolytic fragments are formed. Molecular chaperones influence this process. Tissue data point to amyloid fibrillogenesis in lysosomes and near cell surfaces. A comparison can be made of the fibrillogenesis in prion diseases and in enhanced AA-amyloidosis. In the reactive form, acute phase SAA is the supply of the precursor protein, whereas in the prion diseases, cell membrane proteins form a structural source. Aβ-amyloid in brain tissue of aged dogs showing signs of dementia forms a canine counterpart of senile dementia of the Alzheimer type (ccSDAT) in man. Misfolded proteins remain potential food hazards. Developments concerning prevention of amyloidogenesis and therapy of amyloid deposits are shortly commented.

Key words: Extracellular fibrils, Amyloid, Amyloid enhancing factor, Prion, PrP, Spongiform encephalopathy, Alzheimer's disease

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INTRODUCTION

Proteins are found in each cell and tissue and there is close connection between pathological lesions and changes in proteins. Several structural fibrillar proteins are found within the cells and the extracellular compartment. Pathological lesions of fibrillar microanatomical structures may be accompanied by fibrillar changes. As pathology starts in the necropsy room and ends as science, some examples of lesions observed in morbid anatomy, histopathology, immune histochemistry, ultrastructural pathology, X-ray diffraction (XR), infra red spectroscopy (IR) or circular dichroism (CD), will be mentioned.

After presentation of examples of fibrillar

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proteins in animal pathology, the major part of this paper will be directed to a special group of pathological fibrillar proteins: amyloid.

EXAMPLES OF FIBRILLAR PROTEINS IN ANIMAL PATHOLOGY

Coagulation disorders such as thrombotic lesions, degenerative tissue changes and collagen changes such as scarring, are common findings. Most general pathology books have good chapters on these subjects. Human hematology textbooks outline coagulation and coagulation disorders resulting in fibrin formation.

Cellular fibrillar proteins are well known in histopathology. Many researches have been conducted on the role of cytoskeletal elements: microfilaments, microtubules and the intermediate sized filaments especially important for tumour diagnostics and in daily abattoir pathology (the prostate gland metaplastic epithelium's cytokeratine development is used to monitor treatment with anabolic steroids). In the human brain neurofibrillary tangles form a common lesion associated with disorders such as Alzheimer's disease. Whereas not frequently reported, these tangles sparsely occur in old dogs (Papaioannou *et al*., 2001). Cases of muscular dystrophy, as studied in dogs or in MRY-breed cattle, showed myofibrillary degeneration with central core pathology (Goedegebuure *et al*., 1983; Goedegebuure, 1987). In cases of dermatosparaxis, the extracellular collagen fibrils are targets of morphological studies in many laboratories. Routine electron microscopy is often disappointing, while irregularity in thickness and contour of the fibrils (Brown *et al*., 1993) as well as fibril twisting (Minor, 1980) are frequently encountered features instead of the characteristic hieroglyphic pattern shown in some textbooks (Jones *et al*., 1997) and papers (Abramo *et al*., 1999).

Joints with cartilage degeneration may show fibrillation as indication of proteoglycan loss. The extracellular matrix proteoglycans can be visualized by electron microscopy after cuprolinic blue staining (Niewold *et al*., 1991). Electron microscopy has been used for ultrastructural quality assessment of human cardiovalvular homografts (Goffin *et al*., 1997). Explants of human valves obtained at autopsy years after transplantation from persons who had been living with a well-functioning heart, are known to show loss of cellularity (Goffin *et al*., 1990; Koolbergen *et al*., 1998). In an EC-BIOMED-2 project on the subject of viable cells in the transplants, sheep experiments were performed. Fresh ovine aortic valve homografts, frozen valves and peracetic acid-killed leaflets were implanted in the thoracic aorta of recipient sheep. Six months after implantation, the animals were euthanasied and the valves studied for several variables in different European laboratories. In all the cases, the connective tissue was found to be of more or less medium-fair quality with fair content of proteoglycans, but the original fibroblasts appeared to have been lost (Aidulis *et al*., 2002; Farrington *et al*., 2002; Neves *et al*., 2002). At the graft surface, however, several cell layers had developed. Analysis of similarity between graft and recipient by three DNA microsatellites revealed differences in pattern only in two cases of the peracetic acid-treated group. This indicated donor DNA remained in a graft without histologically visible nuclei after a six months implantation period (Neves *et al*., 2002).

Another example of pathology of fibrillar proteins was in leather with speckles. From frozen skins we processed halves to leather, while the other halves were studied by histopathology. This revealed blood-sucking lice at areas corresponding with the speckles in the leather.

In amorphous deposits, moreover, fibrillar proteins may occur. A major group of electron microscopically fibrillar proteins is found in histopathologically amorphous extracellular deposits, amyloid.

AMYLOID AND VIRCHOW

After Virchow (1854) coined the name, amyloid, for the pathological extracellular material he

found during histopathological examination of human patients, one-hundred-fifty years later we still call it amyloid. He used the word, amyloid, because of iodine staining similarities with extracellular plant material as wood and starch. In 1859 already, Friedreich and Kekulé (1859) described the protein nature of amyloid. Chemical investigations in the second half of the twentieth century revealed a role for glycosaminoglycans and heparan sulphate- (Snow *et al*., 1987; 1995) and/or chondroitin sulphate-containing proteoglycans in amyloid (Niewold *et al*., 1991; Magnus, 1991).

A burst in amyloid research developed after the electron-microscopical discovery of amyloid fibrils in 1958 by Cohen (Cohen *et al*., 1958; Cohen and Calkins, 1959) and subsequent description by others (Spiro, 1959). It offered new possibilities for isolation (Pras *et al*., 1968), peptide separation and analysis of a large series of different chemical amyloid types corresponding to the known variations in clinicopathological patterns, and offered a rational base for nomenclature (WHO-IUIS, 1993; INC, 1998a; 1998b): the first letter, A, for amyloid and one or more others for the chemical type. The first amyloid type characterised was amyloid protein of a group A: AA. The second A of AA stands for the protein-A, with the A simply representing the first letter of the alphabet (Benditt and Eriksen, 1971). AA is derived from the acute phase reactant, serum amyloid A (SAA) which is an apolipoprotein of high-density lipoproteins (HDL), classes 2 and 3 (INC, 1998b; Benditt *et al*., 1979; 1982). It is formed mainly by the liver upon stimulation by pro-inflammatory cytokines (Gruys *et al*., 1994), in particular interleukin-6 (Mihara *et al*., 2004). A second type originally designated group B (Benditt and Eriksen, 1971), soon was called AL, with the L representing light chain because this type appeared to be derived from monoclonal immunoglobulin light chain proteins. At present more than twenty-five types have been characterized, one of which is an isolate of mammary corpora amylacea in bovine milk (Niewold *et al*., 1999a). Alpha-S2-casein peptide was extracted and the amyloid was designated Aα-S2C (Niewold *et al*., 1999a). Recent studies in our laboratory on guanidium chloride-dissolved, water extracted, amyloid fibrils isolated from tissue-derived bovine corpora, on Western blotting revealed a single cross-reacting band corresponding to mammary serum amyloid-A3 (mSAA3) (McDonald *et al*., 2001).

AMYLOID CHARACTERISTICS

Notwithstanding the different chemical types, the insoluble amyloid fibrils were found to share a characteristic ultrastructural morphology of stiff, non-branching, about 7.5–10 nm thick fibrils of undetermined length (Cohen, 1966) with a hydrophobic core (Li *et al*., 1999; Inouye *et al*., 2000). High magnification electron microscopy of the fibrils revealed a superficial twist and two protofibrils (Cohen, 1966). On subsequent X-ray diffraction studies (Eanes and Glenner, 1968) and infrared spectroscopy Glenner *et al*.(1974) described patterns which accord with a high content of antiparallel cross beta pleated sheets as secondary molecular structure for the amyloid types studied (AA and AL). This also clearly has been shown in domestic animal material (Van Andel *et al*., 1986; 1988b). The cross beta pleated sheet became a widely adopted concept, whereas other possibilities such as beta turns and beta helixes to explain the laboratory results, remain (Lazo and Downing, 1998). Glenner (1980) proposed the term beta-fibrillosis to describe the amyloid diseases, but this became never widely accepted. After studying amyloid in central organs, Glenner started with brain amyloids and found the same characteristics in fibrils derived from human Alzheimer plaques (Glenner and Wong, 1984) and in fibrillar material obtained from brains of hamsters with experimental scrapie (Prusiner *et al*., 1983).

On histology, the amyloid deposits showed uniform tinctorial characteristics of which apple green birefringence after staining with Congo red was most specific (Glenner, 1981), and its orange coloured fluorescence is most sensitive (Linke, 2000). Several pathologists tried to classify the different amyloid deposits found. Romhanyi (1971;

1972) succeeded in finding a method to distinguish between major groups by pretreating the sections before Congo red staining. Later on, others used potassium permanganate method (Wright *et al*., 1977) to distinguish AA from non-AA. At present, in most laboratories, polyclonal and monoclonal antibodies are used for immunohistochemistry which can be applied on paraffin sections (Van de Kaa *et al*., 1986) and plastic embedded thin sections for electron microscopy (Niewold *et al*., 1991; Linke *et al*., 1983; Peperkamp *et al*., 1997).

The most frequently encountered amyloid type in veterinary medicine is AA-amyloid. The characteristic deposition pattern in most species is in the central organs such as spleen, liver, enteric mucosa and arterial walls. In *Gallinae* (Landman and Gruys, 1998) it may also be deposited in the joints.

In *Felidae*, pancreatic insular amyloid (AIAPP) is rather common (Ma *et al*., 1998). Other types of amyloid less frequently encountered in animal species, are AapoAI (Roertgen *et al*., 1995) or AApoAII (Gruys *et al*., 1996), localised AL amyloid (Van Andel *et al*., 1988a; Ramos-Vara *et al*., 1998; Platz *et al*., 1997), amyloid in odontogenic tumours (Gardner *et al*., 1994; Breuer *et al*., 1994) or mammary tumours (Taniyama *et al*., 2000) and amyloid in brain tissues: Aβ in old dogs and $AprP^{sc}$ in sheep with scrapie (Van Keulen *et al*., 1995) (>50% in a small series of Dutch cases (Gruys, 1988).

FIBRILLOGENESIS AND THE AMYLOID ENHANCING FACTOR (AEF)

The pathogenesis and formation of amyloid represent an intriguing enigma. Whereas for the characterised types their precursors are known, it is unclear exactly how the transition of alpha helixes and random coils into the beta-pleated sheets occurs. The precursors of some human hereditary forms of amyloidosis represent amyloidogenic mutants, whereas other precursors are totally normal proteins. Numerous experimental investigations have been published regarding different types of amyloid. The first studies (with immunoglobulin light chain proteins and insulin) were under lysosomal pH and proteolytic conditions. Parallel-aligned intralysosomal amyloid, however, also developed in rats after phagocytosis of injected bovine fibril suspensions (Gruys and Castaño, 1977).

Later on, amyloid precursor protein crystallisation upon a beta-sheeted nucleus was described (Kisilevsky *et al*., 1995). The transformation, however, needed a lag time. Working with SAA- or AA-rich solutions, freezing and thawing (own observation) and acidic pH (Kluve-Beckerman *et al*., 1999) were found to trigger fibrillogenesis. Some papers (Seelig *et al*., 1995; Wimley *et al*., 1998; Van Nostrand *et al*., 1998) reported studies of the transition processes of precursors to amyloid fibrils using physical techniques such as circular dichroism and nuclear magnetic resonance (Guijarro *et al*., 1998). From these papers it appears that physicochemical growth of amyloid fibrils by changing the original molecular structure to beta turns, cross beta sheets or beta helixes is a rather simple process. It is mediated by degraded fragments, or by prefibrillar protein species where by molecular chaperones largely may influence the crystallisation process (Dobson, 2004). Amyloidogenic sequence stretches in proteins have been recognised which were validated experimentally (Lopez de la Paz and Serrano, 2004). Short specific amino acid stretches appeared to enhance the amyloidogenesis (Ventura *et al*., 2004) and self replicating beta stranded peptides forming amyloid-like fibrils, have been mentioned (Takahashi and Mihara, 2004). In solutions from different amyloid precursors including SAA, transthyretin, Aβ precursor protein and PrP^{c}, beta pleated fibrils can be formed in particular at lysosomal pH or even high pressure (Torrent *et al*., 2004). Various cofactors such serum amyloid P-component, proteoglycans, apolipoprotein E-4 and calcium ions, are known from animal experiments and in vitro studies (MacRaild *et al*., 2004). Also intracellularly several molecular chaperone pathways are known preventing misfolding (Carver *et al*., 2003; Barral *et al*., 2004).

In animal studies, however, the deposition of amyloid appeared to be not in any case as predicted.

Reaggregation studies of bovine AA-amyloid fibrillar proteins that were separated by gel filtration in guanidium chloride, revealed that, except for the AA protein, material of larger molecular weight was necessary to reobtain congophilic fibrils (Van Andel *et al*., 1986; Hol *et al*., 1983).

In experimental rodents (mouse and hamster) the acute phase SAA was found to be of major importance (Hol *et al*., 1985) and should be kept elevated in concentration by long lasting a reactive stimulus (e.g. by repeated injections of casein, LPS, or silver nitrate) and should represent an amyloidogenic isotype. Amyloid resistant mouse strains were found to have a non-amyloidogenic acute phase SAA (Gonnerman *et al*., 1995; Liang *et al*., 1998). Rats were shown not to form acute phase SAA and AA-amyloid at all (Ren *et al*., 1999; Yu *et al*., 2000).

When induced in the appropriate mice or hamsters, the AA-amyloid was deposited after a lag period which could dramatically become reduced with a single injection of an extract of amyloid-containing tissue, preamyloid tissue or even normal tissue, called amyloid enhancing factor (AEF). This factor was not serine-protease-sensitive and a similar enhancement was obtained after injection of rhTNF-α or poly-I:C (Niewold, 1990), and molecules with preformed beta structure, such as silk (Kisilevsky *et al*., 1999). Acceleration of ATTR amyloidosis with preformed fibrils, however, not developed in mice transgenic for wild-type human transthyretin (Tagoe *et al*., 2004), whereas injection of apolipoprotein A-II fibrils in young senescence-accelerated mice enhanced AApoAII amyloidosis (Higuchi *et al*., 1998; Xing *et al*., 2001).

The AEF was found to represent a low molecular weight glycoprotein which, when isolated from hamster amyloid fibrils (FAEF), contained Congo red-negative beta pleated sheet nuclei (Niewold *et al*., 1987). Murine glycerol-extracted AEF appeared to contain most prominently C-terminally degraded SAA fragments (Magy *et al*., 2003).

The AEF in murine studies had been found to pass the digestive tract barrier (Elliott-Bryant and Cathcart, 1998; Lundmark *et al*., 2002) as did AApoAII in senescence accelerated mice (Xing *et al*., 2001). AEF did not cross the placental barrier in the mouse (Shtrasburg *et al*., 1999).

It is noteworthy that AEF might be necessary for the AA-amyloidogenesis from SAA. Presumably AEF represents a nidus for the crystallisation of the amyloidogenic acute phase SAA and cytokines with a beta sandwich might be involved in the process of formation of the first nidus (Gruys and Snel, 1994). Further on, misfolded SAA-fragments might accelerate the fibrillogenesis. Cathepsin (Cat) B from murine macrophages was found to form amyloidogenic SAA derivatives, whereas Cat D did the opposite (Phipps-Yonas *et al*., 2004). Murine macrophages formed amyloid easily from recombinant SAA when AEF was present (Kluve-Beckerman *et al*., 1999). Best results were obtained after addition of the proteolysis-inhibitor, pepstatin, and AEF (Kluve-Beckerman *et al*., 1999). On cultures of fibroblasts the AEF adhered to the cells and functioned as crystallisation nidus or sink for the recombinant SAA protein (Magy *et al*., 2003).

During electron microscopy of the first deposited amyloid fibrils in the FAEF hamster model, Niewold (Niewold, 1990) discovered ultrastructural changes which accorded with accumulation of SAA antigen at the outer cell membrane and intramembranous AA-fibrillogenesis. Some papers on other types of amyloid mention the cell membrane as template for beta pleated fibrillogenesis (Seelig *et al*., 1995; Wimley *et al*., 1998; Van Nostrand *et al*., 1998) resulting in membrane perturbation and development of cell pathology (Muller *et al*., 1995; Janson *et al*., 1999). Gruys *et al*.(1979), and Niewold (1990) showed vesicular membrane remnants to accompany freshly deposited amyloid fibrils. Intramembranous fibril formation by rearrangement to linearly aligned hydrophobic protein moieties might result in stiff fibrillar areas explaining membrane rupture with amyloid extrusion from the cell surface and vesicles between the amyloid fibrils (Gruys and Snel, 1994).

The above mentioned membrane findings fa-

vour the possibility of amyloid formation as a disorder of cell membranes, making it even more delicate when the precursor protein itself is a normal component of that cellular compartment such as Aβ precursor protein and the cellular PrP.

PRIONS, THE BSE CRISIS

Different from other medical people working on transmissible encephalopathies, Stanley Prusiner chose scrapie in experimental hamsters as subject of his research and conducted chemical investigations on extraction of the agent (Prusiner, 1982), which he found to represent a small peptide, without nucleic acids, which easily formed rods. He coined the name prion for the agent and PrP for the peptide. With the help of Glenner he proved they had amyloid characteristics (Prusiner *et al*., 1983). He showed the agent replicated itself by changing the conformation of the cellular PrP to that of PrP^{sc}, from alpha helix to beta pleated sheets. In the animal experiment it was a process with a long incubation period. Prusiner found the agent in brain and spleen tissue (Prusiner, 1982) Diringer and Ehlers (1984) showed rapid early replication what could be prevented by dextran sulphate-500, a macrophage-inhibitor. Later studies (Brown *et al*., 1999) showed that follicular dendritic cells carry cellular PrP and possibly represent the primary area of concentration increase of the prion. The infectious prion protein that is known to cross the enteric barrier after oral exposure, can be considered to use a toxic mechanism for its replication: changing the molecular folding of its sister molecules in cell membranes carrying these molecules, to beta pleated sheets resulting in more prions.

Prusiner's findings and hypotheses were rapidly adopted in all countries were scrapie was endemic. Discussions on viroids and virinos (Kimberlin, 1982) remained (Schreuder, 1998) and even bacterial agents were proposed (Bastian *et al*., 1981; Wisniewski *et al*., 1996) until the bovine spongiform encephalopathy (BSE) crisis emerged and transgenic mouse experiments proved the agent replication concept (Scott *et al*., 1999). Last critics started to vanish after human patients and cats developed a new variant of Creutzfeldt-Jakob's disease (nvCJD) and feline spongiform encephalopathy (FSE) respectively, both caused by the BSE agent (Pearson *et al*., 1992; Almond and Pattison, 1997; Hill *et al*., 1997; Bruce *et al*., 1997).

The BSE epidemic is considered to have originated from a changed rendering process and the feeding of meat and bone meal to ruminants (Wilesmith *et al*., 1988; 1991). Debate is still ongoing regarding the sheep- or cattle-origin of the prion before it underwent concentration increase by the rendering-feed cycle.

As such, an alimentary infection route functioning as a nidus for its own increase, may be compared with the role of AEF in reactive amyloidosis. That latter factor can pass the gut barrier, but needs a separate supply of amyloidogenic acute phase SAA, whereas the PrP^{sc} finds its substrate in the cell membranes of the lymphoid and nervous systems.

SPECIES AND BREED SUSCEPTIBILITY

Amino acid transpositions in the human PrP protein make subjects prone to spontaneous CJD, with the genetic make up of a single gene explaining their susceptibility (Collins *et al*., 2000). It was also shown that differences in prion susceptibility between breeds of sheep (Belt *et al*., 1995; Hunter *et al*., 1997) or mouse (Bruce *et al*., 1991) depend on their PrP genes. Parry already in 1983 described scrapie in sheep flocks as a genetic disorder (Parry, 1983).

Species barriers were shown to be associated with genetic susceptibility, the amino acid sequence of the middle third (Priola, 1999) of the PrP and, in particular, with glycosylation differences of the prion (Collinge *et al*., 1996; Collinge, 1999). Experiments with transgenic mice resulted in the final proof (Telling, 2000).

Differences in susceptibility to reactive amyloidosis as found in human families (Livneh *et al*., 1997; Tekin *et al*., 2000), Abyssinian and Siamese cats (Van der Linde-Sipman *et al*., 1997; Niewold

et al., 1999b), and brown layer poultry (Landman, 1998) might have a more complex pathogenical explanation. Not only are genes necessary for amyloidogenic SAAs, but also cytokine release/inflammation enhancing genes may be involved; as has been shown in human families with familial Mediterranean fever (FMF) (Livneh *et al*., 1997; Tekin *et al*., 2000).

After *Enterococcus faecalis* injection to induce amyloid arthropathy, brown chickens which were shown to have similar predicted SAA as their less amyloid-susceptible white counterparts (Ovelgönne *et al*., 1999), revealed more polymorphonuclear leukocytes and a weaker CD8+ lymphocyte response than white layers (Zekarias *et al*., 2000). This epiphenomenon fits with old results in murine experimental amyloidosis concerning T-cell suppression. In the chickens, the occurrence of a genetic difference in T-helper reactivity (Th1/Th2-balance) has finally been proposed as important pathogenic factor in their infection-related amyloid-susceptibility/resistance.

CANINE COUNTERPART OF SENILE DEMENTIA OF THE ALZHEIMER TYPE (ccSDAT)

In brain tissue of aged dogs, Alzheimer-like pathology has been encountered with lipofuscin being present in neurons and macrophages, Aβ-precursor protein in neurons, Aβ-positive plaques, 4-hydroxynonenal in neurons and macrophages, and limited intraneuronal accumulation of tau and advanced glycation end products increasing with longevity (Gruys, 1995; Papaioannou *et al*., 2001; Rofina *et al*., 2001a; 2003). A limited number of Gallyas' silver stain positive tangles has been encountered (Papaioannou *et al*., 2001). Reaction of microglia cells and accumulation of macrophages in relationship to the plaques were not obvious. However, a close spatial relationship of the plaques with small blood vessels was observed (Rofina *et al*., 2003). After perfusing the brain arteries with barium sulphate, a decreased filling was found associated with longevity (Rofina *et al*., 2001b). Behaviour scores of aged dogs revealed a group of demented animals. In brain tissue sections and extracts of brain samples of those demented dogs, significantly more lipofuscin-like pigments and carbonyls were measured than in not-demented counterparts, whereas α-tocopherol was decreased (Skoumalova *et al*., 2003). Ongoing correlation studies for pathological and behavioral changes in our laboratory so far, reveal amyloid, oxidative damage product accumulation and cortical atrophy to represent significant markers for dementia. These results favor oxidative tissue damage and nutritional antioxidative components to be of major pathogenical, preventive and therapeutical significance in canine senile dementia of the Alzheimer type.

COMMENTS

From the discussed pathological fibrillar proteins it is clear that the misfolding of the amyloid precursors at present remains the most intriguing problem. Various clinical amyloid deposition-associated disorders (amyloidoses) are known and much is still undiscovered. Preventive and therapeutic interventions may regard stabilisation of precursor proteins, molecules that prevent fibrillogenesis, beta breaker peptides, small carbohydrates interfering with amyloid fibrils and amyloid specific antibodies (Buxbaum, 2004; De Lorenzi *et al*., 2004; Gandy *et al*., 2004; Heppner *et al*., 2004; Hurshman *et al*., 2004; Miller *et al*., 2004; Kisilevsky *et al*., 2004; Permanne *et al*., 2002; Rijkers *et al*., 2002).

The possible implications of the protein folding disorders in food-associated hazards must not to be ignored. With several small outbreaks of BSE in different parts of the world outside Europe, it remains a problem to be solved. In the meantime, tissues with any other type of amyloid should be carefully discarded because of its possible AEF activity and transenteral AA-amyloid accelerating effects (Elliott-Bryant and Cathcart, 1998; Lundmark *et al*., 2002). Cooking may not destroy all beta sheets in AA-amyloid as can be concluded from

pressure and heating studies (Dubois *et al*., 1999).

With increasing age, the pathogenical factors related to brain decay and loss of cognitive capabilities are of major concern. The canine kept as pet dog may be regarded as model for SDAT, which disease together with cancer and cardiovascular lesions represent the major culprits associated with hospital costs and finally death.

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