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Chapter 1

Title: "Amyloid" — Historical Aspects

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Additional information is available at the end of the chapter

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1. Introduction

General agreement prevails today on the contents of the term "amyloid". It refers to "a condition associated with a number of inherited and inflammatory disorders in which extracellular deposits of fibrillar proteins are responsible for tissue damage and functional compromise", as defined in the textbook of pathology [1]. One and half centuries ago, in contrast, the nature of amyloid was the very target of an academic dispute among the leading scientists, European at those days. Curiously, the term "amyloid" has prevailed although in the course of time the concept of amyloid has nearly turned upside down.

2. Origin of amyloid: Matthias Schleiden and botany

The term "amyloid" was brought in the scientific literature by the German botanist Matthias Schleiden (1804 - 1881). Schleiden was born in Hamburg as the son of a Hamburger physician. He first studied laws in Heidelberg and received his pHD in 1826. However, working as a lawyer felt unsatisfactory to him and he turned to study medicine in 1832, in Göttingen and Berlin. Schleiden oriented to botany, microscopy and anatomy, with a special interest in the chemical and anatomical composition of plant cell, and received his second PhD in 1839. One of Schleiden's major ideas was to apply the iodine-sulphuric acid test for starch in plants. This test was originally described in 1814 by Colin and Gaultier de Claubry to show the blue staining reaction of starch with iodine and sulphuric acid [2]. Schleiden presented his discoveries at the scientific meetings of the "Gesellschaft Naturforschender Freunde" and reported on the application of the iodine-sulphuric acid test on plants on the 20th February, 1838 (in: Ostwalds klassiker der exakten Wissenschaften, band 275 Verlag Harri Deutsch (Klassische Schriften zur zellenlehre. Matthias Jacob Scleiden, Theodor Schwann, Max Schulze, text in German), cited in [3]. Scleiden's original interpretation was that the reaction demonstrated the transformation

of the plant material into starch [4]. Schleiden published his several botanical findings in the book form in 1842-43, with the title "Grundzige der wissenschaftlichen Botanik". It is remarkable that the 2nd and 3rd editions of the book, subtitled as "Die Botanik als inductive Wissenschaft behandelt" were also translated in English in 1849, with the name "Principles of Scientific Botany" and "Botany as an Inductive Science", reflecting the attraction that Schleiden's observations woke also outside Germany. In the above mentioned book Schleiden first time uses the term "*amyloid*" for starch, referring to"starch-like". The word itself stems from the latin word "*amylym*" for starch. Schleiden describes "amyloid" to represent "a normal amylaceous constituent in plants" [2], as shown in the straight citing from the English translation of the book [5] below.

"Amyloid is, when dry, a cartilaginous, but moist, gelatinous, clear, transparent body, soluble in boiling water, strong acids, and caustic alkalies, but not in ether and alcohol in a concentrated state. It is coloured blue by iodine, and the combination is soluble in water, giving it a golden-yellow colour. It is found only in the layers of the primary cell-membrane. There is no chemical analysis of this substance. It has been found at present only in the cotyledon-cells of Schotia latifolia,S. speciosa, Hymencea Courbaril, Mucuna urens, M. gigantea, and Tamarindusindica."

The application of the iodine-sulphuric acid test on plants was not the most remarkable among Schleiden's scientific discoveries. Based on his interest in microscopic studies he got the unique idea that plants are made of cells, and that the growth of plants depends on the production of new cells. To get to this idea Schleiden was also lucky. In Berlin he had met Theodor Schwann (1810 - 1882), another great scientist of those days who had made similar observations in animals [6]. The published observations of Schleiden (1838) and Schwann (1839) form the basis for the unified "cell theory", applicable to all living organisms. During the same time (1839) the French chemist Anselme Payen (1795 - 1878) described a substance in woods that resembled starch. This substance reacted with iodine-sulphuric acid test similarly to starch, and Payen named it "cellulose". The iodine-sulphuric acid reaction became later on a standard procedure used by botanists to demonstrate the presence of cellulose in woods [4].

It is well possible that amyloid deposits have been described even earlier, in the reports on human autopsy cases with homogenous material in liver or spleen tissue [2], probably representing amyloid. The first observation stems from the year 1639, described by Nicolaus Fontanus.

3. The term "amyloid" in the medical literature: Rudolf Virchow

Whereas Matthias Schleiden was the first to use the term "amyloid" in botanics, it was the German pathologist Rudolf Virchow (1804 - 1881) who applied it in the medical literature. Virchow studied medicine and anatomy in Berlin and Würzburg, and was graduated in 1843.

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Virchow was interested in microscopic studies, similarly to Schleiden. Virchow used the word "amyloid" first time in 1854 in his publication "Über eine in Gehirn und Rückenmark des Menschen aufgefundene Substanz mit der chemischen Reaction der Cellulose", in Virchow's Archiv für Pathologische Anatomie and Physiologie und fur klinische Medicin. Berlin 6; 354-368; 1854 [7]. In this paper Virchow described the small round deposits in the nervous system (Figure 1) with the mention that those structures showed the same color reaction with iodine and sulfuric acid, i.e. a change from brown to blue, typical to starch. Therefore, Virchow was convinced that those structures were identical to starch [8]. Virchow named those structures "corpora amylacea", similarly to Schleiden (the name based on the Latin term "amylum" for starch, see previously). Later Virchow applied the iodine sulphuric acid test to other tissues infiltrated with amyloid. The representatives of the French and British Schools instead considered amyloid to be more closely related to cellulose [2]. They use the name "lardaceous" (based on the bacon-like appearance of the tissue, French School) and "waxy" (based on the homogeneity of the material, British School). They could also use the term "sago" (a sweet substance in certain palm species).

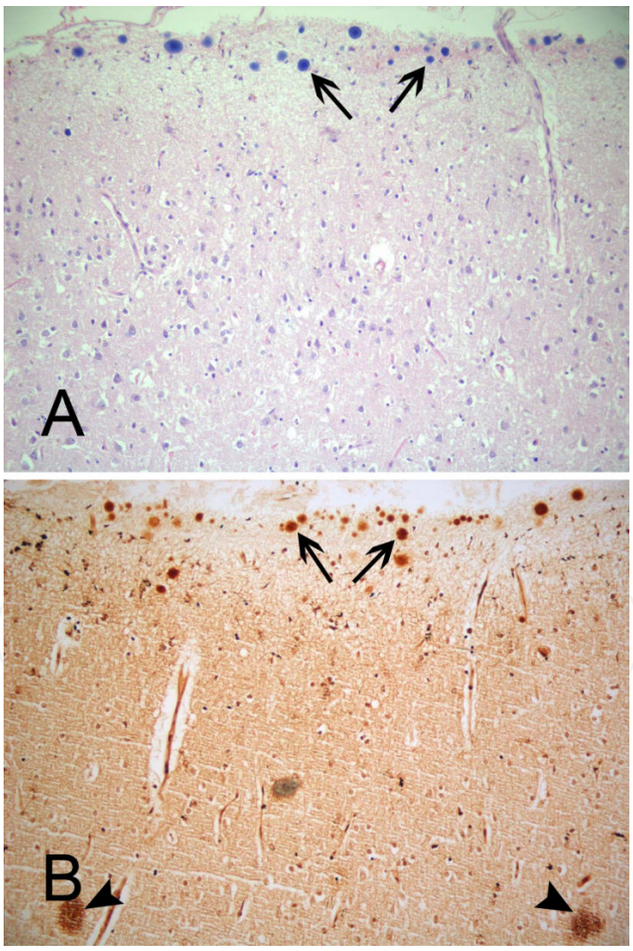

Figure 1. Corpora amylacea (arrows) stain blue in H&E (A) and brown in methenamine-silver (B) stain which also reveals a few senile plaques of diffuse type (B). Diffuse plaques do not contain amyloid. The patient was 104-year old female suffering from vascular dementia. Original magnification x 200.

Virchow developed an observational and experimental view on medical sciences. In this regard he resembled the French and British scientists at that time but contrasted to the more speculative German scientific tradition. As Virchow's writings received an unfavorable attention in German journals he decided to found in 1847 a journal of his own "*Archiv für pathologische Anatomie und Physiologie und für klinische Medizin"* with another German pathologist, Benno Reinhardt. The bearing idea of the new journal was not to publish papers containing "outdated, untested, dogmatic or speculative ideas". After Reinhardt's death in 1852 Virchow edited the paper alone, with the name "Virchow's Archives", a world-famous and respected journal still today.

Virchow's investigations in pathology extended to several other clinically significant issues. For instance, he discovered the mechanism of thromboembolism and developed the standard method of autopsy, as described in "The handbook on special pathology and therapeutics" in 1854. Further, in addition to Schleiden and Schwann, Virchow was the third scientist who has been nominated as an inventor of the "cell theory". He applied the concept in humans and published it in "Cellular pathology" in 1859. Yet, the probably most significant of Virchow's ideas was that he understood to combine the macroscopic and microscopic pathologies with clinical manifestations of disease [9].

Virchow was not only a pathologist. His interest and knowledge extended to anthropology, archeology, politics and social sciences [10]. For instance, Virchow established the first hospital trains bringing medicine in the battlefields, and he also was the first to understand the influence of poor hygiene on the spread of contagious illnesses. Political and social activities combined with huge scientific career brought to Virchow the status as the world-renowned physician and "Father of pathology".

4. The end of the 1800's: Progress in the staining methods to detect amyloid

A new insight into the biochemical character of amyloid was presented in 1859 when the prominent German chemist August Kekulé (1829 - 1896) reported on the high proportion of nitrogen in organs infiltrated with amyloid [2,11]. Kekulé assumpted that the material mainly represented "albumoid" compounds. In addition, he did not find material corresponding chemically to "amylon" or cellulose." Virchow never agreed with Kekulé, criticizing his method to analyze the whole tissue specimens (e.g. liver). After Virchow's opinion, convincing results necessitated a method to isolate the amyloid substance first [2]. Indeed, also in this he was ahead of his time. After more than one hundred years other constituents such as glycosaminoglycans and heparan sulphate [12,13] and chondroitin sulphate -containing proteoglycans [14,15] were identified as additional, albeit minor components of amyloid deposits [16].

In contrast to Virchow, Kekulé's observation on high nitrogen contents of amyloid were accepted by several scientists, including the British physician Samuel Wilks (1824 - 1919) who had collected more than 60 cases with the white, "stony", "gelatinous" or "lardaceous" visceral material, i.e. amyloid detected at the autopsy [2]. George Budd, another British internist (1808

- 1882) actually got the same result than Kekulé when analyzing the chemical composition of a pale autopsy liver [2].

There was another novel invention that Virchow did not accept: the metachromatic stains. In 1875 three scientists; the French pathologist and histologist Victor Cornil (1837 - 1908) in Paris, the Austrian anatomist Richard Heschl (1824 - 1881) in Vienna and Rudolf Jürgens in Berlin described independently the usefulness of methylviolet stain to detect amyloid. Already next year, in 1876, Soyka reported having found amyloid in the cardiac tissue with the use of this new method (Soyka J. Prag Med Wschr 1: 165, 1876; cited in Hodgkinson and Buerger [17,18]). William Ackroyd and Paul Ehrlich described methylviolet stain as "metachromatic" in 1878. Metachromatic stains challenged Virchow's iodine sulfuric acid test for decades [2] but were eventually replaced by Congo red.

5. Development of contemporary staining methods: Congo red dye and fluorescence microscopy

Reactivity with Congo red stain or "Congophilia with apple green birefringence" was the first criterion for amyloid [11], introduced by the Belgian Physician Paul Divry (Divry P. Etude histo-chimique des plaques seniles. J de Neurologie et de Psychiatrie 27:643-57, 1927, cited in Sipe [11]). Congo red dye itself was invented by the German chemist Paul Böttiger in 1884 (Böttiger P. Deutsches Reich's Patent 28753, August 20, 1884, cited in Frid [19]). Congo red is an aniline dye, originally created and used for staining textiles. Böttiger developed the first "direct" dye that did not require additional substances for fixation to the textile fibers. The owner of the patent, the AGFA Corporation developed the name "Congo" to the new dye after the diplomatic conference that was ongoing in Berlin just at that time (1884 - 1885). The goal of the "Congo conference" was to mediate a trade dispute between several European colonial powers in the Congo River Basin in Central Africa [2,20]. The name "Congo" referred to an exotic place that was on the tip of the lips, and proved to be effective for marketing purposes [2,20]. In addition to staining textiles Congo red was actually used to stain tissues already in 1886 [20]. However, it was not until in the year 1922 when the young German chemist Herman Bennhold discovered the capacity of Congo red to bind to amyloid (Bennhold H. Eine spezifische Amyloidfärbung mit Kongorot. Münchener Medizinische Wochenschrift (November):1537-1538, 1922; cited in Kyle [2]). In 1962 Puchtler described the renewed method for the use of Congo red in histological preparations [21].

The Puchtler modification [21] of Congo red staining is widely used in pathology as the first step in detecting amyloid in histological specimens. Of course, individual laboratories may apply their own variant of the method. Congo red staining is also applicable to frozen sections and for staining devices. In the diagnostic purposes the formalin-fixed histological samples are generally embedded in paraffin, sectioned 5-8 μm thick slices, stained with Congo red, and viewed in a light microscope under polarized light in which amyloid can be seen as red to green birefringent homogeneous material.

(Figure 2). Interestingly, the light microscope finding has been observed to vary in different types of transthyretin (TTR)-related amyloidosis and accordingly the distribution into two different histological patterns of amyloid deposition (designed as A and B) has been proposed [22]. In pattern A, seen in senile systemic amyloidosis (SSA) and in some cases with TTR-related familial amyloidosis, there is weakly congophilic, homogenous amyloid material that is patchy distributed. In pattern B, detected in a part of patients with TTR-related familial disease, strongly congophilic amyloid appears as thin streaks. Thus, the biochemical structure of amyloid fibrils can be transmitted to the microscopic finding.

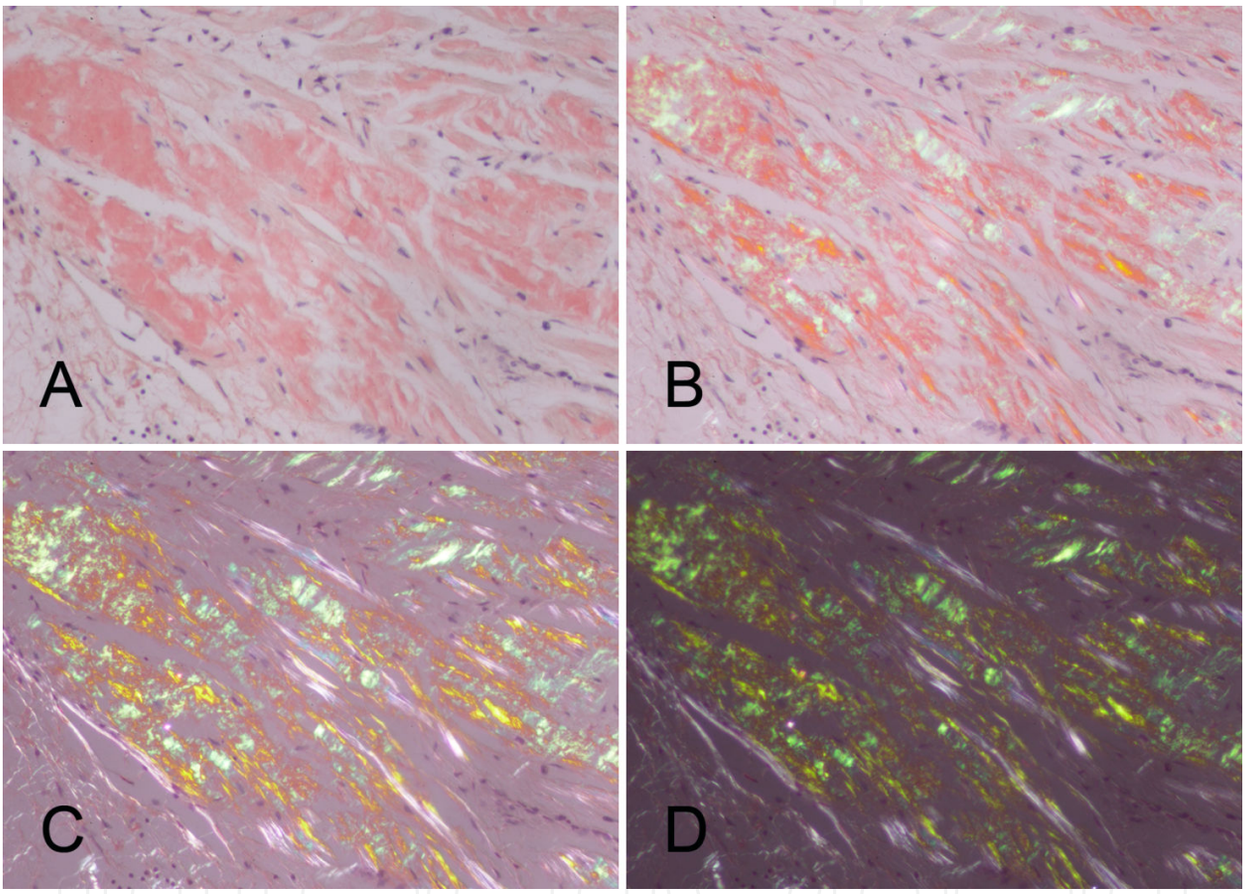

Figure 2. The red colour (A) of amyloid in the cardiac tissue of a patient with senile systemic amyloidosis (SSA) gradually (B,C) turns to green (D) in the polarized light. Original magnification x 400.

The chemical name of Congo red, also known as "direct red", "direct red 28", or "cotton red", is 3,3'-[(1,1′-biphenyl)-4,4′-diylbis(azo)] *bis*-(4-amino-1-naphtalene acid) disodium salt ($C_{32}H_{22}N_6O_6S_2$ 2Na). It is a symmetrical molecule with the molecular weight of 696.7 g/mol and the diameter approximately 21Å [23]. The molecule has a hydrophobic center composed of two phenyl rings that are linked via diazo bonds to two charged terminal naphtalene moieties. The terminal parts of Congo red contain sulphonic acid and amine groups. Congo red exists in chinone form in acidic solution, and in sulphonazo form in basic solution, changing the color from blue (below pH 3) to red (above pH 5). Thus, Congo red can be used as a pH indicator

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as well. The binding of Congo red to amyloid induces a characteristic shift in the maximal optical absorbance of the molecule from 490 nm to 540 nm. The mechanisms of interaction between Congo red and amyloid fibrils has been intensively studied [24,25] but the process is not completely understood [19]. Congo red binding has been assumed to depend on the secondary, β-pleated configuration of the fibril, possibly mediated by hydrophobic interactions of the benzidine centers as well as the electrostatically charged terminal groups [19].

Amyloid can also be visualized using the fluorescence microscope. Fluorescence microscope is a light microscope used to study the properties of organic and inorganic substances with the aid of the phenomena of fluorescence and phosphorescence. The component of interest in the specimen is labeled with a fluorescent molecule, the "fluorophore". Amyloid can be detected using thioflavin stains (Thioflavin-T or -S) which emit green fluorescence when they are bound to amyloid. Thioflavin-T (Basic Yellow 1 or CI 49005) is a benzothiazole salt, obtained by methylating dehydrothiotoluidine with methanol in the presence of hydrochloric acid. When the dye binds to β sheets it undergoes a 120 nm red shift of its excitation spectrum that may selectively be excitated at 450 nm, resulting in a fluorescence signal at 482 nm. Thioflavin-S is a mixture of compounds resulting from the methylation of dehydrothiotoluidine with sulphonic acid. The fluorescence method is specific for amyloid similarly to Congo red [26] and very sensitive. The disappearance of fluorescence during time can be regarded a disadvantage of the method, because the reaction cannot be re-examined later.

6. The beginning of the 1900's: Alzheimer's disease and associated pathologies

In 1907, Aloysius (Alois) Alzheimer described "senile" plaques and neurofibrillary tangles in a demented patient. Today we know that the plaques represent *extracellular* amyloid derived from amyloid beta (Aβ) protein whereas the neurofibrillary tangles represent *intracellular* amyloid formed on tau protein.

Alzheimer (1864 -1915) was German psychiatrist, born in Bavaria. He got his medical education at the universities of Tübingen and also in Berlin and Würzburg, similarly to Virchow, to receive his medical degree in 1887. Soon thereafter he began to work in a mental asylum "die Städtische Anstalt für Irre und Epileptische" in Frankfurt am Main. Alzheimer's scientific interest focused on pathology of the nervous system, especially anatomy of the cerebral cortex. He collaborated with the neuropathologist Franz Nissl (1860 - 1919) and learned Nissl's method of silver staining of the histological sections. In the year 1901 Alzheimer happened to get the 51 -year old Mrs. Auguste Deter to be his patient at the Frankfurt Asylum. Mrs. Deter had a very unusual clinical picture with loss of short-term memory and odd behavioral symptoms. In 1902 Alzheimer moved to work with his colleague, another German psychiatrist Emil Kraepelin (1856 - 1926) at the University of Heidelberg. Kraepelin had, similarly to Alzheimer, special interest in neuropathology. Both moved to Munich next year. Mrs Deter died in 1906 in Frankfurt, and Alzheimer decided to bring her brain and medical records to Munich for neuropathological study. He grasped to apply Nissl's method of silver staining on the

histological sections of Mrs. Deter's brains, and thereby identified the neurofibrillary deposits in the atrophic brain. The first report of the extraordinary pathological findings was presented in the same year at the University of Tübingen, prior to the appearance of the publication in 1907 (Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift für Psychtiatrie und Psychisch-gerichtliche Medizin. 1907 Jan; 64:146-8).

The original histological sections on which Alzheimer based his description were rediscovered in the 1990^{ies} in Munich. This gave the unique opportunity to re-evaluate his work [27]. Silver stains have been used to diagnose Alzheimer's disease (AD) during decades and the original observations made by Alzheimer's and Kraepelin are valid even today. Quite recently, techniques using the immunohistochemistry (IHC) -based techniques in the diagnosis of AD pathology have also been introduced [28]. Alzheimer's neuropathological discoveries were not restricted to AD pathology. For example, he also described the loss of nerve cells in the corpus striatum in Huntington's disease and brain changes in epilepsy [29].

Mrs. Deter suffered from a syndrome that is called today as *presenile* dementia. Presenile dementias form a group of hereditary dementia syndromes which are often autosomally dominantly inherited. It has turned out that presenile dementia syndrome is quite common in the population called Volga Germans (VG). VG stems from people who emigrated in the 1760 s from the German Hesse area around Frankfurt to the southern Volga region in Russia. During the late 19th and early 20th centuries many of the descendants of VG emigrated to US. Presenile dementia of the VG is due to the mutation N141I in the gene for presenilin (PSEN) 2 [30]. Interestingly, neuropathology of the brains of subjects with this mutation is similar to Mrs. Deter's case [27]. Therefore, especially as Mrs. Deter was living in the Hesse area in Germany, an idea was got that she would have belonged to the population of VG. Mrs. Deter's brain tissue was tested for the presence of the PSEN 2 mutation – but the result was negative [31]. Yet, this does not preclude that Mrs. Deter would have had a different mutation in PSEN 2 or a mutation in other genes such as PSEN 1 or APP.

Although the diagnosis of Mrs. Deter is still open, Alzheimer's paper was a starting point to enormous amounts of experimental and applied investigations of AD, an old age associated dementia syndrome. The disease belongs to the major causes of death in the western world, and it is estimated that about 24 million people suffer from it worldwide [32]. In spite of the huge work, the etiology of AD is still uncertain. Several hypotheses have been proposed [33], of which the "amyloid cascade hypothesis" by John Hardy and Gerald Higgins [34] has maybe got the greatest attention. The theory has recently also been criticized [35] as many therapeutic attempts based on it have failed [36].

The first descriptions of AD pathology were based on silver staining (Figure 3A) without no idea about the biochemical composition (Figure 3B) or relationship to amyloid of such structures (Figure 3C,D). Plaque amyloid however was discovered relatively soon (in 1927, see previously) by Divry after Bennhod had published his application of Congo red in tissue (in 1922, see previously). Cerebrovascular amyloid (cerebral amyloid angiopathy, CAA), detectable in 80-90% in the brains of patients with AD was first time reported by Greek Pantelakis in 1954 [37].

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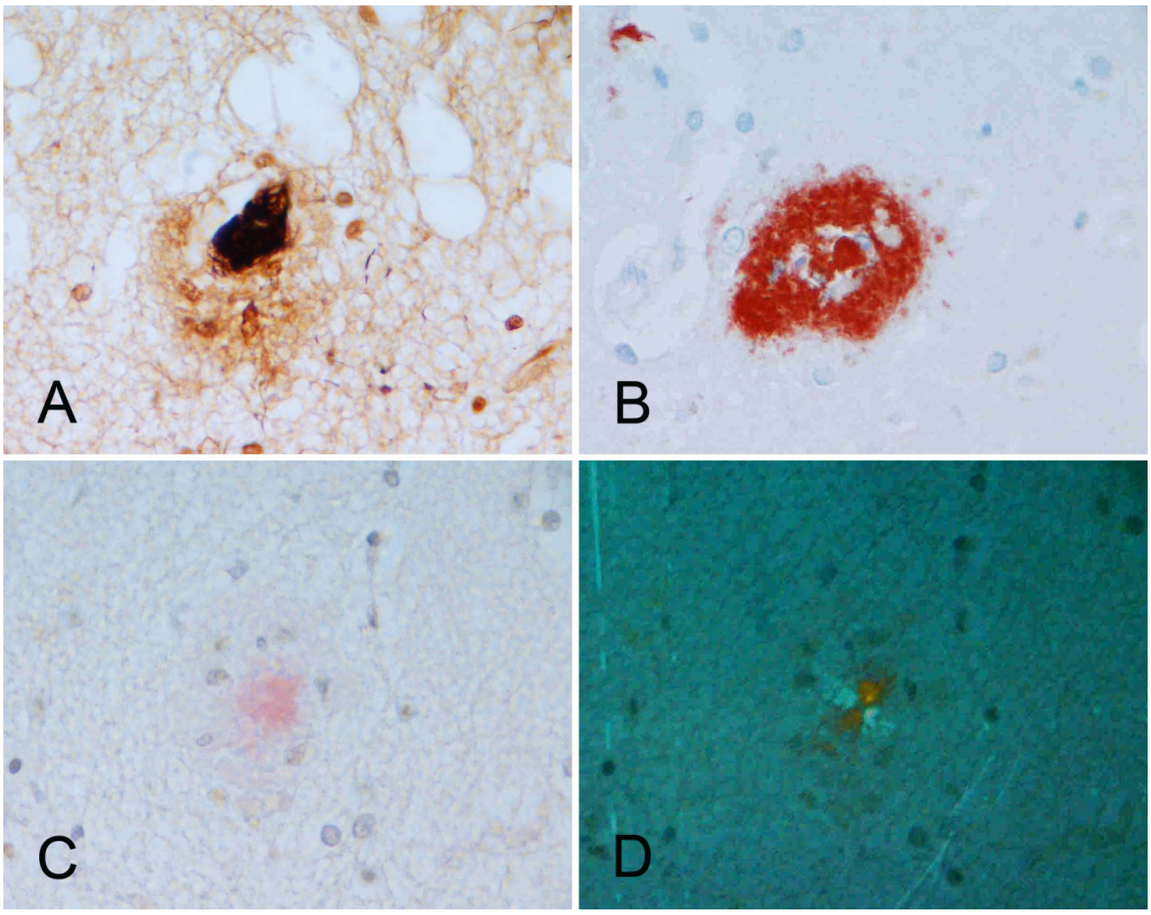

Figure 3. A senile plaque with amyloid core stained with methenamine-silver (A), immunohistochemistry against Aβ (B) and Congo red (C without and D with polarization) stains. Original magnification x 600.

7. Identification and extraction of the amyloid fibril

After the 2nd world war amyloid research stretched from Europe to include also Northern America and Japan. A substantial advance in the field took place in the late fifties. Two American researchers, Alan S Cohen from Harvard Medical School in Boston and Evan Calkins from Massachusetts General Hospital reported on the fibrillary structures in the samples of several types of amyloids in 1959 using electron microscopy (Cohen AS and Calcins E. Electron microscopic observations on a fibrous component in amyloid of diverse origins. Nature 183 1202-3, 1959; cited in Vinters [38]). Several attempts followed to isolate the fibrils from tissues and organs. Cohen and Calkins themselves described the first extraction method. It consisted of gentle physical separation and homogenization of the material in saline, followed by low-speed centrifugation. This yielded a layer of fibrils not present in the sedimentation pellets of normal tissues and demonstrated a green birefringence in polarized light after staining with Congo red [39]. The next method was published by George Glenner and Howard Bladen (NIA, Bethesda, Maryland). They had extracted amyloid fibrils using alkaline sodium glycinate in 1966 [40].

A significant step forward took place when M Pras (originally from the Tel Hashomer Hospital, Tel Aviv, Israel) and colleagues from New York University School of Medicine described the method to extract proteins from amyloid-laden tissues using water [41]. Spleen tissue from a deceased patient with "primary" (i.e. AA) amyloidosis was homogenized with physiological saline (NaCl), and the mixture was centrifuged. The sediment was next homogenized with NaCl several times to remove most of the soluble proteins and other soluble materials. Salt was then removed by homogenizing the residue in distilled water, followed by centrifugation of the suspension. Lastly, the residue was homogenized in distilled water and centrifuged four times to give a supernatant rich in protein. Adding Congo red dye and NaCl then resulted in a gelatinous precipitate with the typical green birefringence, demonstrating that the supernatant represented soluble amyloid.

The "water extraction method" of Pras has been widely used to extract almost all types of amyloid except for Aβ and prion protein amyloid [42,43]. The method was revolutionary in amyloid research as it enabled (1) identification of the β-pleated sheet configuration of amyloid proteins and (2) discovery of the biochemical structure of those proteins.

8. The β-pleated sheet configuration

In nature, most proteins have both α-helix and β-pleated sheet secondary structure. In the amyloid form, the proteins are mostly in the β-pleated sheet conformation though not exclusively. Factors that may influence changes in the spatial form of proteins include increased protein content, low pH, metal ions proteins that are associated with amyloid deposits but are not part of the insoluble fibrils themselves, also called " chaperones" [44]. The secondary structure of amyloid consists of the polypeptide backbone, mostly in the β-pleated sheet conformation, oriented perpendicular to the fibril axis. This β-pleated sheet structure was revealed by X-ray diffraction analysis of isolated amyloid protein fibrils by Eanes and Glenner in 1968 [45-47].

9. Identification of the different amyloid proteins

The major consequence of the invention of the water extraction method of Pras was the identification of the biochemical composition of several kinds of amyloids. Glenner and his colleagues soon applied the method to the "primary" (today: AL) amyloidosis [48] and found the relationship between this amyloidosis and immunoglobulin light chains. AL amyloidosis is a neoplastic disease and belongs to the clinically most significant amyloid -related conditions.

During the subsequent years, a long list of amyloid proteins was identified one after another. Inflammation-associated amyloidosis, previously called the "secondary" and today AA amyloidosis, was shown to be caused by amyloid protein A, an acute phase protein in 1972 [49]. Serum protein A was thereafter soon identified in blood [50,51]. In 1978, prealbumin (transthyretin, TTR) was found to be the protein constituent of amyloid deposits in Portuguese familial

amyloid polyneuropathy (FAP) [52], the clinical condition having been described already in 1951 (Corino de Andrade, M. Preliminary note on an unusual form of peripheral neuropathy. Rev Neurol (Paris) 85: 302-6, 1951; cited in Kyle [2]). Similar diseases were found especially in Japan and Sweden in the subsequent decades. The Finnish type of familial amyloidosis, today known as AGel amyloidosis, was described in 1969 by the Finnish ophthalmologist Jouko Meretoja [53]. In 1980, TTR was characterized as the amyloid protein also in "senile cardiac amyloidosis" (SCA) [54], later renamed as senile systemic amyloidosis (SSA) [55,56]. In 1983, the Icelandic type of familial cerebral amyloid angiopathy (HCHWA-I) was found to be related to cystatin-C protein [57]. Next year, 1984, the first report on the AD-associated Aβ protein was published two Glenner and Wong who identified Aβ in the cerebrovascular tissue [58]. Colin Masters (Australian), Konrad Beyreuther (German) and colleagues described the same protein one year later, in 1985, in the plaques (Figure 3B). Japanese Fumitage Gejyo described beta 2 -microglobulin as the amyloid fibril protein in the dialysis-related amyloid arthropathy in the same year [60]. Tau protein of the neurofibrillary tangles was identified in 1986 in the laboratory of Henryk Wisniewsky in New York by Inge Grundke-Iqbal and colleagues [61].

The nature of islet amyloid polypeptide (IAPP) was discovered by Swedish pathologist Per Westermark from University of Uppsala and his colleagues in 1986 [62,63]. In 1988, apolipoprotein A1 (APOA1) was characterized as the amyloid protein in the hereditary amyloid disease in Iowa, USA [64]. In 1990, two groups discovered independently that amyloid fibril protein in the Finnish (AGel) amyloidosis was related to gelsolin [65,66] and identified the causative Asn-187 mutation in the gene for gelsolin [67,68]. The first description of a genetic cause for a hereditary amyloid disease was already published several years earlier, as the Japanese Satoru Tawara and colleagues identified the point mutation in the gene coding for TTR leading to the substitution of methionine instead of valine at position 30 in TTR-related FAP in 1983 [69]. Development of the polymerase chain reaction (PCR) –based techniques have accelerated the identification of mutations in the genes of the amyloidogenic proteins, and today more than one hundred different mutations have been described in the TTR gene. Most of the mutations lead to clinical disease with the deposition of amyloid in different organs.

In the past two decades three different proteins were characterized describing three novel different familial amyloid diseases with a preference for renal manifestation: fibrinogen A-α chain [70], lysozyme [71] and apolipoprotein AII [72]. The last identified amyloid fibril protein, also presenting with renal amyloidosis especially in Mexican Americans, was leucocyte chemotactic factor 2 [73].

10. Prion diseases

Characterization of the prion protein (PrP) in 1982 [74] opened up a new perspective in the amyloid reseach. Scrapie, a prion disease in sheeps and cows, was described in Spanish merino sheeps already in 1732 [75] but it took two and a half centuries to detect the causative agent. Scrapie belongs to prion diseases, also referred to "transmissible protein misfolding disorders" [76]. The highest degree in the conformational shift from α-helix to β-sheet structure occurs in

the genetically determined form (Gerstmann-Straussler- Scheinken disease) and in PrP - associated CAA [77].

Prion diseases occur in several mammalian species and can be sporadic, hereditary, or acquired. The disease exists in nine different types in humans. The first known descriptions of human prion disease appeared independently in 1920 and 1921 by Creuzfeld and (Creutzfeldt HG: Über eine eigenartige herdformige erkrankung des Zentralnervensystems. Z gesamte Neurol Psychiatr 1920, 57: 1-19) and Jacob (Jacob A: Über eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befunde. (Spastische Pseudoskleros- Encephalomyelopathie mit disseminierten Degenerationsherden). Z Gesamte Neurol Psychiatr 1921, 64: 147-228.), cited in Imram [76]). This has formed the basis for the contemporary name of the disease: "sporadic Creutzfeldt –Jacob's disease".

Two Australian anthropologists, Ronald and Catherine Berndt, were the first to describe the peculiar disease occurring in the Fore linguistic group of people in the Australian Pretectorate of New Guinea, today Papua-New Guinea. Vincent Zigas, the district medical officer started to study the disease in 1957 with the young American virologist and pediatrician Carleton Gajdusek who was interested in infectious diseases. The clinical picture of the disease, as described in the article: "Degenerative Disease of the Central Nervous System in New Guinea — The Endemic Occurrence of Kuru in the Native Population" [78], cited in Libersky [79], consisted of headache and pain, cerebellar ataxia, tremors, shivering and choreiform or athetoid movements. The disease, named as "kuru", occurred exclusively in that Fore linguistic group people and was due to the ritualistic cannibalism ("transumption"). Kuru was neuropathologically characterized with neuronal degeneration, myelin degeneration, astroglial and microglial proliferation and plaque formations [80]. Interestingly, another human prion disease presenting with similar plaques occurred in Western Europe four decades later. The disease, first reported in UK in 1996 by British investigators and called as "variant CJD" [81] however manifested differently. The typical features of variant CJD include agitation, aggression, apathy and paranoid delusions [81]. BSE (Bovine spongiform encephalopathy) prions were soon shown to be causally linked with variant CJD [82].

The American scientist Stanley Prusiner purified the prion protein (PrP Scr) from sheep in 1982 [83]. The name "prion" was based on the letters of the word *Pro*te*in*aceus. Prusiner assumed that PrP would act solely in the protein level without influence of any genetic material, as it had been proposed several years previously [84]. This and several other several issues are still open, such as if there are factors rendering cells capable of replicating prions and propagating them to the nervous system, and if PrP is fully infective without any cofactors [85]. Gajdusek (in 1976) and Prusiner (in 1997) were honored with Nobel Prize in Medicine for their work in prion diseases.

11. Nomenclature

The modern nomenclature of different types of amyloids (Table 1) is based on the amyloid fibril protein. An originally informal amyloid nomenclature committee was established in 1974

Amyloid protein	Precursor protein	Type	Syndrome (Involved tissue)
AA	(Apo)serum AA	S	Reactive, previously: "secondary"
AANF	Atrial natriuretic factor	L	(Cardiac atria)
AApoAI	Apolipoprotein AI	S, L	Familial (aorta, meniscus)
AApoAII	Apolipoprotein AII	S	Familial
AApoAIV	Apolipoprotein AIV	S	Sporadic, aging
ABri	ABriPP	S	Familial dementia, British
ACal	(Pro)calcitonin	L	C-cell thyroid tumors
ACys	Cystatin C	S	Familial
ADan	ADanPP	L	Familial dementia, Danish
AFib	Fibrinogen α-chain	S	Familial
AGel	Gelsolin	S	Familial, previously: "Finnish"
AH	Immunoglobulin heavy chain	S; L	Myeloma-associated, previously: "primary"
AIAPP	Islet amyloid polypeptide	L	Insulinomas, aging, previously: "amylin" (Islets of Langerhans)
AIns	Insulin	L	Iatrogenic
AKer	Kerato-epithelin	L	Familial (cornea)
AL	Immunoglobulin light chain	S; L	Myeloma-associated, previously: "primary"
ALac	Lactoferrin	L	(Cornea)
ALect2	Leukocyte chemotactic factor 2	S	Mainly kidney
ALys	Lyspzyme	S	Familial
AMed	Lactadherin	L	Aortic and arterial media, aging
AOAAP	Odontogenic ameloblast-associated protein	L	Odonogenic tumors
APro	Prolactin	L	Prolactinomas, aging (pituitary gland)
APrP	Prion protein	L	Spongiform encephalopathies (brain)
ASemI	Semenogelin I	L	(Vesicula seminalis)
ATTR	Transthyretin	S,L?	Familial, SSA (localized: tenosynovium)
Aβ	Aβ protein precursor (AβPP)	L	Aging, AD, CAA
Aβ2M	β2-microglobulin	S; L?	Hemodialysis-associated (localized: joints)

S = systemic; L = localized; SSA = senile systemic amyloidosis; AD = Alzheimer's disease; CAA = cerebral amyloid angiopathy.

Table 1. Human amyloid fibril proteins and their precursors.

in Helsinki, Finland, in connection with the 1st International Symposium on Amyloidosis. The 1st official nomenclature committee was founded at the 3rd international symposium on amyloidosis in Povoa de Varzim, Portugal (1979). Thereafter the committee (the Nomenclature Committee of the International Society of Amyloidosis) has met several times to create the official nomenclature lists for each types of amyloid. The last meeting took place in 2010 in Rome, Italy (2010), in conjunction with the 12th International Symposium on Amyloidosis [86]. The reports of the meetings are published in "Amyloid", the official journal of amyloid diseases.

To be included in the official nomenclature list, the amyloid fibril protein fibril must have been unambiguosly characterized and described in a peer-reviewed journal. The present nomenclature list contains 27 fibril proteins capable to cause human disease. Nine of them have been tested in animals. There are also at least and six proteins appearing as *intracellular* inclusions, with all or some properties of amyloid [86].

12. The clinical diagnosis of amyloidosis

The diagnosis of the depositon of amyloid in diverse clinical conditions has traditionally needed a tissue sample stained with Congo red or thioflavin compounds, followed by the definition of the fibril protein using the IHC-based techniques. These techniques, using commercially available antibodies are quite well applicable in most of the clinically significant amyloid diseases.

The usage of radiological techniques to detect amyloid deposits started in 1988 when Philip Hawkins (London) reported on the usage of in vivo radiological techniques using the ^{123}I labeled serum amyloid P component (SAP) in mice [87]. Two years later the same technique was applied successfully in humans [88]. Recently, antibodies to human SAP molecule were even shown to have potential therapeutic properties in both mice and humans [89], based on the ability of the antibodies to trigger a giant-cell reaction to eliminate visceral amyloid deposits. Another milestone in the radiological diagnostics of amyloid diseases was the discovery by Klunk and colleagues (University of Pittsburgh, US) of the ^{11}C-labeled PET tracer "Pittsburgh compound B" (PiB) to bind selectively to fibrillar Aβ [90]. This made it possible to reveal amyloid pathology *noninvasively* in subjects with AD pathology. Yet, the half-time ($T_{1/2}$) of ^{11}C is very short (about 20 min) and therefore not applicable in clinical use. The recent invention of a comparable ^{18}F-labeled tracer with much longer $T_{1/2}$ (110 min) is expected to expand the applicability of PET in a larger number of patients. Of the potential ^{18}F-labeled tracers tested, ^{18}F-AV-45[91] seems to be the most promising [92].

13. Conclusion

The concept of amyloid has transformed several times during the nearly two century long research history of the issue. It is now clear that the cerebral corpora amylacea that inspired

Virchow so greatly are mostly composed of glycogen-like substances with sulfate and phosphate groups. In this regard, Virchow actually was right. On the other hand, it has also turned out that those structures do not represent amyloid. Therefore, it can be asked why the term "amyloid" still has prevailed. The most apparent explanation is Virchow's standing as one of the most valued scientists of his time and probably also the iodine staining that was used for a long time as the diagnostic test for amyloid [93].

Amyloid research has traditionally related to the diagnosis and clinical manifestations of the deposition of amyloid in the tissues and organs in diverse disease conditions. Applications in other branches of science such as biotechnology may outline the future prospects in the amyloid field [94].

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