

# A Historical Analysis of the Quest for the Origins of Aging Macula Disorder, the Tissues Involved, and Its Terminology

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**ABSTRACT:** Although ocular tissues involved in aging macula disorder (AMD) were already known in 300 BC, the last type of photoreceptors was discovered only 10 years ago. The earliest descriptions of AMD appeared around 1850. It took over 150 years, till a clearer concept of AMD was formulated and even longer to grasp its pathophysiology. The uncertainty of researchers about the pathogenesis of AMD over the last century is reflected in its changing terminology. The evolution of this terminology is provided in a table to afford the reader a better insight into explanations proposed by researchers during this quest.

**KEYWORDS:** ageing macula disorder, age-related macular degeneration, AMD, F.C.Donders, Junius-Kuhnt, A.Nagel, Ophthalmic history, senile macular degeneration

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## Introduction

Without a clear concept of a disease, it is hardly possible to perform good research, such as epidemiologic and genetic. For example, amyotrophic lateral sclerosis was described in 1874, and eluded for decades genetic researchers, until it was found to comprise over 20 different disorders. I suspect that the same may hold for open-angle glaucoma. Only since 1970 we know substantially more about aging macula disorder (AMD). However, I discovered that the first descriptions of AMD, although under a different name, appeared in 1852. It took over a century and a half before a clearer conception of AMD emerged, and its high prevalence, as well as its impact on the quality of life of many elderly people, was appreciated.

The purpose of this article is to give an historical overview of the earliest descriptions of retinal and surrounding tissues associated with AMD. I also comment on earlier theories about their functions. Next, the later development of its terminology is reviewed, which partly reflects the pathophysiological considerations over time. In a historical medical investigation, one may adopt a strictly chronological approach or a more anatomical one. I preferred the latter to avoid a jumble of dates and medical terms. Therefore, the different historical facts relevant to each adjacent layer of the eyeball, from the sclera to the retina, are mentioned. An overview of

the anatomy of the eye around the start of our era may be found elsewhere.<sup>1</sup>

## The Choroid

The choroid was known before the retina and seems to have been drawn by Democritus of Abdera around 400 BC.<sup>2</sup> He named the outer coat of the posterior pole of the eye *chitoon puknotatos* (dense tunic) and its inner coat *chitoon malista somphos* (more spongy tunic). About 100 years later, Hippocrates replaced the term dense outer tunic of the eye with *to leukon* (the white) and divided the spongy tunic into the two parts: an outer *meninx leptotera* (delicate membrane) and an inner *arachnoeides* (the cobweb like), all encircling *to hugron* (the moist).<sup>2</sup> Thus, both the spongier tunic and its outer delicate membrane appear to have been what we now call the choroid. The ancient Greeks did not use the word *chorion* for our choroid; the chorion was a membrane enclosing the fetus in the womb, the afterbirth, or the membrane on the inside of the egg-shell. The name chor(i)oeides chitoon (tunic like a chorion) in the eye appears for the first time in Celsus at the start of our era.<sup>2</sup>

The human choroid adheres to the sclera with a lamina fusca (dark brown layer), a loose cellular tissue with elongated pigmented cells. In 1722, Ruysch<sup>3</sup> demonstrated the detailed



choroidal vasculature, in drawings of choroidal casts he made with a secret wax formula, 40 years before Haller. Modern textbooks, nevertheless, mention that the choroid is divided into the large vessel layer of Haller, the smaller vessel layer of Sattler (who mentioned nine layers in the choroid), and the choriocapillaris. According to Eschricht,<sup>4</sup> Hovius<sup>5</sup> first described the choriocapillaris. On translating Hovius's Latin text, however, I could not find a capillary layer or membrane mentioned in it.<sup>6</sup> In any case, the name choriocapillaris was coined by Eschricht.<sup>4</sup> Henric Ruysch called the choroidal layers tunica Ruyschiana, to honor his father Frederik, but on close reading, this tunic seems to be a collective name for the choroid, the choriocapillaris, the retinal pigment epithelium (RPE), the tapetum, and Bruch's membrane (BrM).

### The Retina

It remains unclear why the name arachnoeides (like a cobweb) which Hippocrates gave around 350 BC to the layer surrounding to hignon (the vitreous) was changed later to amfiblesteroeides chitoon (tunic like an amfiblestron). Amfiblestron at that time had seven meanings, and one of these, casting net, was arbitrarily preferred above encircling wall or bond (of the vitreous) for retina, hence the word rete (net) in retina.<sup>1</sup> The word retina was coined around 1150 AD in a Neo-Latin translation of an Arabic text.<sup>7</sup> In his *Coliget*, Ibn Rushd Averroes (1126–1198) might have attributed photoreceptor properties to the retina, and he was possibly the first to suggest that the principle organ of sight was the arachnoid membrane (aranea).<sup>8</sup> His work led to much discussion in the 16th century Europe as to whether the principle organ of sight was the traditional Galenic crystalline humor or the Averroist aranea. Platter<sup>9</sup> claimed in 1583 that the retina and not the lens was the light-sensitive organ in the eye. Nearly 100 years later, van Leeuwenhoek<sup>10</sup> mentioned *clootgens* at the end of the fibers of the optic nerve spreading in the eye, which transmitted visible objects to the brain. He used the word *clootgens* in Dutch both to indicate cells and fat globules. The translation of *clootgens* as *globules* in his letter to the Royal Society in London simply may have blurred this distinction. About 150 years later, the photoreceptors were rediscovered,<sup>11</sup> and K lliker<sup>12</sup> separated cones and rods in the human retina as two types

of photoreceptors. It was only in 2002 that a third type was described, photosensitive ganglion cells.<sup>13</sup>

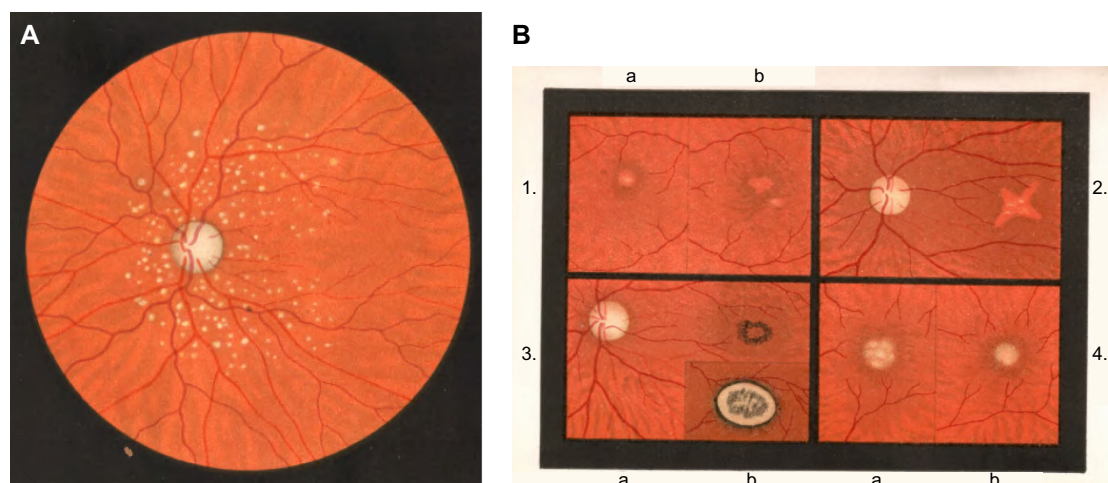
### Bruch's Membrane

Let us now first consider BrM, and the RPE with their AMD-associated changes, before moving on to the macula. BrM is an extracellular matrix between the choriocapillaris and the RPE and may be considered to belong both to the choroid and the retina. Bruch<sup>14</sup> described this membrane, which was named after him, in his monograph of 1844 on granular pigments in vertebrates. Bruch wrote that Eschricht had already described this membrane in the seal six years earlier. Eschricht actually mentioned an extremely thin, serous membrane between the choriocapillaris and the retina (Table 1), so BrM should have been called Eschricht's membrane.<sup>4</sup> Early researchers noticed that BrM becomes thicker around age 70 years.<sup>15</sup> It thickens over time by 135% whether signs of AMD are present or not.<sup>16</sup> Histologically, half of 13 eyes with disciform macular degeneration (dMD) had ruptures in BrM, which were crossed by new vessels.<sup>17</sup> So for about 80 years, people knew that changes in BrM were associated with neovascularization and what we now call wet late AMD. BrM has a basement membrane on both sides and three inner layers,<sup>18</sup> and only recently three types of multilaminar sub-RPE hyperreflectivity were detected with optical coherence tomography in the inner, the outer, or both layers of BrM in eyes with regressing drusen.<sup>19</sup>

Drusen, the hallmark of AMD, were first described in 1854 by Wedl<sup>20</sup> who had no idea where they came from or what they indicated. Their connection with AMD remained obscure for over a century, and even Haab who first coined the term senile macular illness (Fig. 1) explicitly denied that drusen had anything to do with this disorder. Around 1850, three authors, Wedl, Frans Donders, and Heinrich M ller, gave drusen different labels (Table 2). Wedl named them colloid bodies of the choroid and thought that they were incompletely developed cells, because they had no cell membrane or nucleus.<sup>20</sup> Donders called them colloid balls surrounded by pigment, noting their preference for the macular area. He was convinced that drusen originated from the nuclei of the pigment cells, which he believed to belong to the choroid.<sup>21</sup> M ller mentioned deposits on the inner side of the choroid

**Table 1.** Various names for Bruch's membrane in chronological sequence.

YEAR	AUTHOR	ORIGINAL NAME	ENGLISH TRANSLATION
1838	Esricht (4)	Ser�ser Haut	Serous skin, membrane
1844	Bruch (14)	Zarte, glashelle, structurlose Membran	Soft, structureless membrane, clear as glass
1854	M�ller (15)	Glaslamelle der Chorioidea; Strukturlose Lamelle an der Innenfl�che der Chorioidea	Choroidal glass lamella; Structureless lamella on the choroidal inner plane
1871	Rudnew (22)	Glask�rper der Choroides	Vitreous body of the choroid
1874	Hutchinson (42)	–	Lamina elastica of the superficial structures of the choroid
1884	Masselon (25)	Membrane (couche) vitreuse de la choro�de	Glasslike membrane (layer) of the choroid
1915	Axenfeld (31)	Lamina vitrea	Glass layer



**Figure 1.** (A) Drusen of the vitreous membrane of the choroid. Haab wrote: These drusen, also a change in old age, have nothing to do with the macular illness depicted here and should be distinctly separated from this.<sup>54</sup> (B) Images of senile macular disease: (1a and 1b) macula of right and left eyes from a 70-year-old person; (2) legend absent;<sup>54</sup> (3a) beginning signs of disease and (3b) 6 months later; and (4a and 4b) right and left eye from a 74-year-old female.<sup>54</sup>

**Table 2.** Various names for drusen in chronological sequence.

YEAR	AUTHOR	ORIGINAL NAME	ENGLISH TRANSLATION?
1854	Wedl (20)	Colloidkörper von der Chorioidea	Colloid bodies of the choroid
1855	Donders (21)	Colloidkugeln	Colloid balls
1856	Müller (15)	kugelig-drusigen Körper; Druse	Ballshaped, drusenoid bodies; druse
1868	Nagel (44)	Krystalle; Krystalldruse	Crystals; crystal drusen
1874	Hutchinson (42)	–	“Colloid” excrescences from the lamina elastica
1875	Nagel (45)	Glashäutige Wucherungen	Proliferations of the glass membrane
1884	Masselon (25)	Excroissances verruqueuses de la choroïde	Warty growths of the choroid
1896	Oeller (62)	Verrucae laminae vitreae	Warts of the glass membrane

that had a ball-shaped or drusenoid form. In this 1856 article, he coined the word *druse*. He thought that drusen originated from thickenings of the structureless membrane on the choroidal inner side behind the pigment cells.<sup>15</sup> Druse is the German word for geode, a cavity in rock filled with crystals, and Müller probably chose this name because of the crystalline core in some large drusen. Later, the theory was formulated that drusen originate from leucocytes.<sup>22</sup> It is striking that 160 odd years on, we still do not know where exactly drusen originate from. The latest candidate again is the RPE,<sup>23</sup> as Donders suggested. Over the years, several

subtypes of drusen were discovered, one of the most recent being reticular, cuticular, or pseudodrusen.<sup>24</sup>

Around 1884, drusen were even thought to be the cause of *posterior* glaucoma because drusen usually were located around the optic disk, leading to the assumption that thickening of the glasslike layer around the choroidal ring hampered the outflow of ocular fluid.<sup>25</sup> This view was supported by the fact that drusen as well as glaucoma normally were present in both eyes of old persons.

### The RPE

Mondini<sup>26</sup> described in 1791 an actual net-shaped membrane composed of numerous interlinked, black globules, and thus was the first to mention the RPE. He also wrote that Malpighi told Valsalva that the inner side of the choroid was lined by small black globules. Mondini already thought that the pigment served to dampen stray light rays and to attach the retina to the pigment layer. His son Francesco added that the pigmented globules were polygonal that there were no blood vessels between this pigmented layer and the retina and that the black pigment possibly was iron oxide because it was heavier than water and was attracted by a magnet.<sup>27</sup> Around 1820, Jacob<sup>28</sup> confused many authors by referring to a membrane under the retina, running from the optic nerve to the ciliary processes, and this led to a *tiring discussion* according to Eschricht.<sup>4</sup> On rereading Jacob, one has no idea what he meant, although Bidder thought that Jacob’s membrane was the rod layer of the retina. In the first description of the RPE as *the membrane of the pigment*, hexagonal cells were mentioned that were circular in the human fetus and in albino animals.<sup>29</sup> Bruch<sup>14</sup> gave an elaborate description of the RPE and was struck by its monolayer and regular, hexagonal shape. He pointed out that the cones were standing directly on the RPE cells without any membrane or structure between them

and that they had a pigment sheath. Donders mentioned in 1855 RPE atrophy between groups of drusen.<sup>21</sup> It gradually became clear that the RPE could become hypertrophied and after fibrous metaplasia could contribute to fibrous tissue in disciform lesions.<sup>17,30–32</sup>

Basal laminar or basal linear deposits are located between the cell membrane and the basement membrane of the RPE and are often present before drusen appear. These terms were not used in the original electron microscopic descriptions of these deposits.<sup>33</sup> Gass<sup>32</sup> called them “eosinophilic material between an irregularly thickened BrM and overlying degenerated RPE”. Shortly later in 1970, Sarks identified three types of deposits,<sup>34</sup> and it seems that she coined the term basal linear deposit.<sup>35</sup>

### The Macula

In 1782, Buzzi described the macula lutea after dissecting the eyes of a 35-year-old man in the following terms. Thus, in a point lateral to the optic nerve, and also in a healthy condition, one may often see that the retina is colored yellow, be it rather vague.<sup>36</sup> Soemmering<sup>37</sup> thought in 1796 that the macula was a hole in the central retina surrounded by a yellow ring, but soon later, it was mentioned that the macula was just a thin spot in the retina.<sup>38–40</sup> Cuvier<sup>38</sup> wrote that the macula had no color in the neonate but was yellow in the adult. The exact size of the macula was a matter of long discussion, and the area of the central fovea was calculated to be 0.12 mm<sup>2</sup> in accordance with its capillary-free zone.<sup>41</sup>

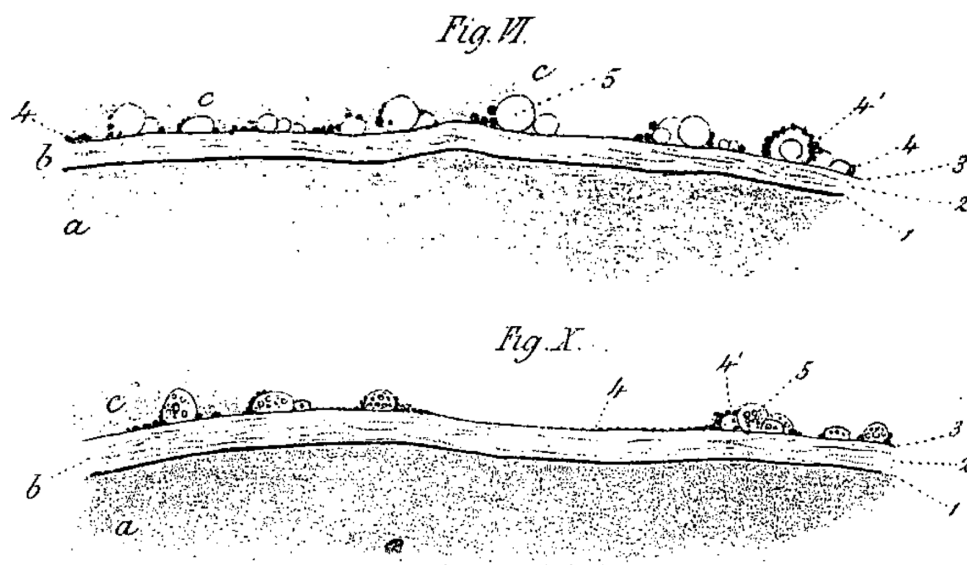
### First Reports on AMD

The pathogenetic process underlying AMD is still not clear, or the tissue primarily involved in it. It seems generally accepted that thickening of BrM and drusen formation in BrM and the RPE, as well as RPE detachments and subretinal

hemorrhages, precede retinal changes of a secondary nature like photoreceptor loss and scarring.<sup>17,42,43</sup>

In his early medical career, Donders performed many autopsies. From 1852 on, he realized the gap in understanding between what he saw using the ophthalmoscope (for a few months in his possession) and the microscope. So he started collecting *healthy* postmortem eyes for histology. In 1855 after examining 38 apparently healthy eyes, he wrote “An important question is in how far the degeneration described here (in the retina), can lead to visual disturbances”.<sup>21</sup> Using microscopy, he noticed rods, obliquely oriented, around small drusen as well as degeneration of the choriocapillaris and the RPE. Rods and cones often were absent above drusen that sometimes penetrated the retina halfway, without expanding the retina on the vitreous side. Drusen compressed the retina (Fig. 2) and rarely were absent in the eyes of persons aged 70–80 years. In none of the eyes he examined postmortem, the visual acuity had been carefully recorded before death. However, Donders considered that the anatomical relation of the drusen to the retina and the degeneration of the RPE had to have an influence on retinal function. He was convinced that the white flecks that he had seen several times with the ophthalmoscope in the eyes of old people suffering from *senile amblyopia* (as loss of visual acuity in the elderly was called at that time) were not fatty metamorphoses but colloid degenerations.<sup>21</sup> An enviable clinical insight on his part.

Nagel<sup>44</sup> was probably the first to publish on AMD, using both clinical and histological data from the same patient. In 1868, he published on a 64-year-old woman with a dark-red net and partly confluent white flecks around both maculae who complained about marked *amblyopia*, metamorphopsia, and a quivering image. Fine brilliant specks were seen with ophthalmoscopy, creating the impression of *Krystalldrusen*. In 1874, the patient complained about more metamorphopsia.



**Figure 2.** Large drusen 5 pressing against the retina (c). a is choroid, b is probably Bruch's membrane, and c is retina in which drusen protrude.<sup>21</sup>



This involved, for instance, human legs appearing bent. Nagel<sup>45</sup> published again on this and two more cases in 1875. The visual fields of these patients were normal, and the eyes were never painful or inflamed. His first patient died at age 73 years due to an abdominal tumor; the eyes were enucleated 27 hours postmortem, and one was put in Müller's fixative. In the nonfixated eye, there were small, sparkling irregularities in the posterior pole on the inner side of the choroid. Flecks around these irregularities were created by thickening of the elastic layer where the dissolved drusen had been and the outer retinal layer over them was markedly thinner. Nagel thought that this could explain the metamorphopsia

and amblyopia the patient complained of. So Donders and Nagel described drusen that caused degeneration of the choriocapillaris, the RPE, and thinning of the neuroretina with vision loss without, however, formulating a concept of macular degeneration (MD).

### Descriptions of AMD from 1855 Onward

Table 3 lists the huge variety of terms, which have been applied to what was probably AMD during the last 160 years. Only those that seem relevant, either because of their widespread use or because of the pathophysiological concept they indicate, will be commented on.

**Table 3.** Terminology of ageing macula disorder (AMD) from its very beginning†.

YEAR	AUTHOR	ORIGINAL NOMENCLATURE	ENGLISH TRANSLATION
1855	Donders (21)	Entartung der Chorio-capillaris und der Pigmentschicht; Amblyopia senilis	Degeneration of the choriocapillaris and the pigment layer; senile amblyopia
1868	Nagel (44)	Über chorioiditis areolaris und über Krystalle im Augenhintergrunde	On areolar choroiditis and on crystals in the ocular background
1874	Hutchinson (42)	–	Symmetrical central chorio-retinal disease occurring in senile persons; Tay's central guttate choroiditis (65)
1875	Nagel (45)	Hochgradige Amblyopie, bedingt durch glashäutige Wucherungen und krystallinische Kalkablagerungen an der Innenfläche der Aderhaut	Advanced amblyopia caused by proliferations on the glass membrane and crystalline lime deposits on the choroidal inner face
1875	Pagenstecher (49)	Chorioido-Retinitis in Regione Maculae Luteae	Chorioretinitis in the region of the macula lutea
1878	Michel (71)	Ueber Geschwülste des Uvealtractus	On tumors of the uveal tract
1884	Nettleship (47)	–	Central senile areolar choroidal atrophy
1884	Nettleship (46)	–	Central guttate choroiditis
1884	Masselon (25)	Infiltration vitrée de la rétine	Vitreous retinal infiltration
1885	Haab (52)	Erkrankungen der Macula Lutea; senile Maculaerkrankung	Illnesses of the macula lutea; Senile macular illness
1887	Goldzieher (48)	Ueber die Hutchinsonsonse Veränderung des Augenhintergrundes	On Hutchinsonian changes in the posterior pole of the eye
1888	Haab (53)	Ueber die Erkrankung der Macula lutea. Senile Macula-Erkrankung	On illness of the macula lutea; Senile macular illness
1892	Caspar (72)	Seniler Degeneration in der Gegend der macula lutea	Senile degeneration in the region of the macula lutea
1893	Fuchs (55)	Retinitis circinata	Circinate retinitis
1897	Goldzieher (57)	Hutchinson'sche Veränderung des Augenhintergrundes (Retinitis circinata Fuchs)	Hutchinsonian change of the eye fundus. (Fuchs' circinate retinitis)
1897	Walker (73)	–	New growth in the macular region
1899	Oeller (62)	Chorio-Retinitis centralis. Anastomosis arterio-venosa	Central chorioretinitis. Arteriovenous anastomosis
1899	Silcock (50)	–	Choroidal gumma
1899	Yarr (74)	–	Central chorio-retinitis resembling an optic disc
1903	Jessop (75)	–	Tumour in region of yellow spot
1904	Batten (59)	–	Peculiar symmetrical swellings in the macular region
1904	Oeller (70)	Degeneratio maculae luteae disciformis	Disciform macular degeneration
1905	Possek (60)	Senile Maculaveränderung bei Arteriosklerose	Senile macular change in arteriosclerosis
1911	Lawford (76)	–	Subretinal new growth of doubtful nature

(Continued)

Table 3. (Continued)

YEAR	AUTHOR	ORIGINAL NOMENCLATURE	ENGLISH (TRANSLATION)
1912	Mosso (77)	Degenerazione disziforme della Macula	Disciform degeneration of the macula
1913	Heinrici (78)	Degeneratio circinata retinae (Ret. circinata Fuchs)	Retinal circinate degeneration (Fuchs' circinate retinitis )
1915	Axenfeld (31)	Retinitis externa exsudativa	External exudative retinitis
1915	Van der Hoeve (58)	Retinitis exsudativa externa	External exudative retinitis
1916	Hegner (79)	Retinitis exsudativa	Exudative retinitis
1919	Elschnig (51)	Tumorähnliche Gewebswucherung in der Macula lutea	Tumor-like tissue proliferation in the macula lutea
1920	Nöthen (80)	Tumoren in der Maculagegend; Retinitis exsudativa haemorrhagica Coats	Tumors in the macular region; exudative hemorrhagic retinitis of Coats
1923	Coppez (61)	Rétinite exsudative maculaire sénile	Senile exudative macular retinitis
1926	Junius, Kuhnt (63)	Die scheibenförmige Entartung der Netzhautmitte (Degeneratio maculae luteae disciformis) Scheibenförmige Erkrankung der Netzhautmitte	Disciform degeneration of the retinal center (Disciform macular degeneration) Disciform illness of the retinal center
1926	Fuchs' Salzmann (81)	Senile Makuladegeneration; Zentrale senile Retinochoroiditis	Senile macular degeneration; central senile chorioretinitis
1937	Verhoeff (17)		Senile disciform degeneration of the macula
1944	Laird (82)		Senile macular degeneration
1959	Maumenee (83)		Serous and hemorrhagic disciform detachment of the macula
1966	Duke-Elder (64)		Senile macular degeneration; Senile macular chorioretinal degeneration; Senile macular degeneration of Haab; Senile disciform degeneration of the macula of Junius and Kuhnt
1967	Gass (32)		Disciform detachment of the neuroepithelium; Senile disciform macular detachment; Senile macular degeneration; Senile macular choroidal degeneration
1969	Straub (66)	Altersbedingte Makuladegeneration	Age-determined macular degeneration
1977	Wessing (84)	Exsudative senile Makulopathie	Exudative senile maculopathy
1985	Folk (85)		Aging macular degeneration
1987	Sunness (67)		Age-related macular degeneration
1992	Klein (86)		Age-related maculopathy
1995	Bird (87)		Early and late age-related macular degeneration; Dry and wet late age-related macular degeneration
1996	Holz (88)	Altersabhängige Makuladegeneration	Age-dependent macular degeneration
1997	Paglianni (89)		Age-related macular disease
2004	De Jong (90)		Ageing macular disease
2006	De Jong (43)		Aging macula disorder
2014	Camelo (68)		Autoimmune macular disease

**Notes:** †Only the first time, a certain concept that was encountered is given here in chronological sequence, unless for different (historical) reasons.

In 1874, Hutchinson<sup>42</sup> described a choroid, “speckled with minute dots of yellowish white deposits”. He considered the spots to be “colloid excrescences of the lamina elastica” and wrote “There is no doubt that the disease is confined to the choroid in the first instance, while the great defect of sight which accompanies it points to implication of the retina secondarily.” He formulated the following three stages in the disease: (1) scattered yellow-white spots; (2) coalescence of these to patches with irregular borders; and (3) hemorrhage

at the yellow spot and absorption of the blood. Essentially, his formulation had anticipated the present-day paradigm of the clinical course from drusen to late AMD. His first three cases dealt with a family, in which three sisters who had experienced the onset of disease at the ages of 40, 48, and 57 years.<sup>42</sup> He actually described Doyme's honeycomb retinal dystrophy, given the rather early age of onset and the fact that there were other cases of visual loss in the family. Hutchinson ended his account by mentioning that his friend Mr. Waren Tay “made

the ophthalmoscopic examination, and drew my attention to the peculiarities presented". In 1884, Nettleship<sup>46</sup> had already noticed central guttate choroiditis, with a plate that clearly showed drusen, so what we now would name early AMD (Fig. 3A). He also published in the same year on central senile areolar choroidal atrophy, now called dry late AMD (Fig. 3B).<sup>47</sup> Soon later, AMD was referred to as "Hutchinsonian changes of the posterior pole of the eye".<sup>48</sup> Goldzieher reported on four eyes of unspecified age with drusen-shaped flecks around the macula and assumed that the changes were due to atheromatosis. Unlike Hutchinson, he did not consider these changes a choroidal disorder, or colloid excrescences of the vitreous membrane of the choroid, but compared them with cerebral leukomalacia caused by occlusions of the macular arterioles. In subsequent years, diagnoses such as chorioretinitis,<sup>49</sup> syphilis<sup>50</sup> and tumors<sup>51</sup> most likely were referring to AMD. Thus, the choroid gradually loses attention as the tissue where these diseases originate from and researchers focus on pathophysiological concepts such as atheromatosis, infections, and tumors.

Although Nettleship<sup>47</sup> had already mentioned central senile areolar choroidal atrophy, Haab<sup>52</sup> was the first to report one year later in 1885 on *Senile Makulaerkrankung* (senile macular illness), as a separate entity among the MDs, starting in the RPE (Fig. 1B). No other articles by Haab have come to light, explaining why he decided that senile macular illness was a separate entity. He concluded from analyzing over 50,000 patient files that this senile macular illness was about as frequent as traumatic ones and *myopic macular affection*. Senile illness was often bilateral, and one should be wary of the outcome of a mature cataract operation when the fellow eye had this illness.<sup>53</sup> It is striking that Haab explicitly stated that drusen, "quite innocent changes in old persons", had nothing to do with senile macular illness (Fig. 1A).<sup>54</sup>

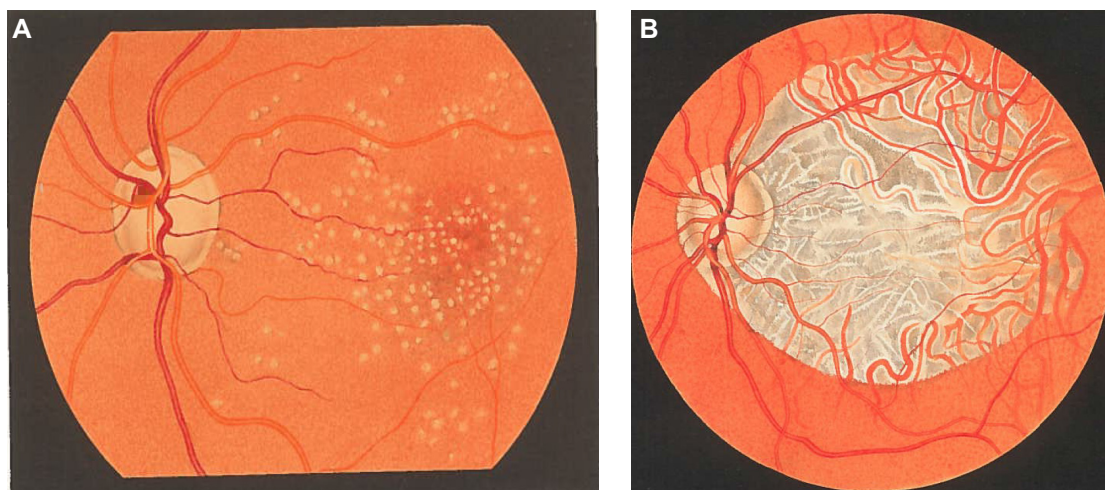
An article in 1893 by Fuchs on circinate retinitis, a circle of white flecks around the fovea,<sup>55</sup> precipitated an avalanche of over 50 articles on this topic.<sup>56–58</sup> Circinate degeneration<sup>57</sup>

or senile exudative retinitis were proposed as more precise terms.<sup>58</sup> A review on 61 out of 129 eyes with disciform MD (dMD) having white spots showed that 36% had circinate retinitis.<sup>17</sup> In 1904, 30 years after Hutchinson's article, sub-retinal hemorrhages in AMD came again to the attention of researchers<sup>59</sup> and one year later, atherosclerosis was suggested as a possible cause.<sup>60</sup> Also fibrous plaques in the macular area of old persons, in conjunction with punctate yellowish dots, followed by hemorrhages, were drawn and described as senile exudative macular retinitis.<sup>61</sup>

In the legend accompanying the image of the eye of a 79-year-old man from Oeller's<sup>62</sup> atlas (Fig. 4), the word *disciform* appears to have been used in 1896 for the first time. The first image of disciform macular disease (dMD) was prob-



**Figure 4.** Disciform macular degeneration.<sup>70</sup> Male, 79 years old. Round center, over 2.5 diopter prominence.



**Figure 3.** (A) Central guttate choroiditis<sup>46</sup> and (B) central senile areolar choroidal atrophy.<sup>47</sup>

ably image number 6 in Pagenstecher's atlas from 1875 called "choroido-retinitis in the region of the macula lutea" (Fig. 5).<sup>49,63</sup> One should not confuse this idea of a disk under the macular area with the clinical expression *disciform reaction*, introduced later, and meaning any development of a neovascular membrane under the macula, whatever its cause. The breakthrough in relation to *disciform MD*, however, was the classic monograph by Junius and his predecessor Kuhnt.<sup>63</sup> They described exhaustively 10 cases with an age range from 36 to 76 years, having a disciform process including five monocular ones, each with a good fellow eye. One case received a diagnosis *illness* of the retinal center, one case received *degeneration* of this center, and eight cases had both diagnoses. Junius and Kuhnt concluded that circinate retinitis and disciform disease of the retinal center belonged to one large cluster of diseases. Only Case I had increasing drusen-like spots along the inferior temporal venule, and the term druse or colloid body did not otherwise appear in any description of their cases. The word *senile* appeared once in Case II with *senile vessel diseases*. The causes suggested for the dMDs varied from alcoholism and lues to hypertension and atherosclerosis. This monograph is valuable for the following three reasons: first, the excellent overview of the past literature on dMD; second, the detailed color drawings; and, finally, it informed the wider public about dMD.<sup>63</sup> On page 132 of the epilog, they wrote: The expression disciform illness of the retinal center may appear somewhat bleak or dull. Would this be the reason that they changed the title of their monograph from *Erkrankung* (illness) to *Entartung* (degeneration) in order to attract attention? So what I always

considered to be a monograph on end-stage AMD was actually a monograph on dMD caused by different retinal disorders, including a few cases with late AMD. Verhoeff and Duke-Elder added the word *senile* to the original title of this monograph of Junius and Kuhnt and started a sub-chapter with "Senile disciform degeneration of the macula (*of Junius and Kuhnt*)". But in doing so, they incorrectly linked all the various causes of dMD with AMD.<sup>17,64</sup> The limited knowledge of or interest in AMD around 1965 may be apparent from *Duke-Elder's System of Ophthalmology*. It covered AMD in seven pages in the chapter "Uveal manifestations of systemic diseases", under the sub-head "Vascular sclerosis", using the terms "Senile macular chorioretinal degeneration, Senile macular degeneration of Haab (Haab named it senile macular illness), or Senile macular degeneration".<sup>64</sup> Drusen were dealt with in a few pages under the subcategory *secondary degenerations*.<sup>65</sup>

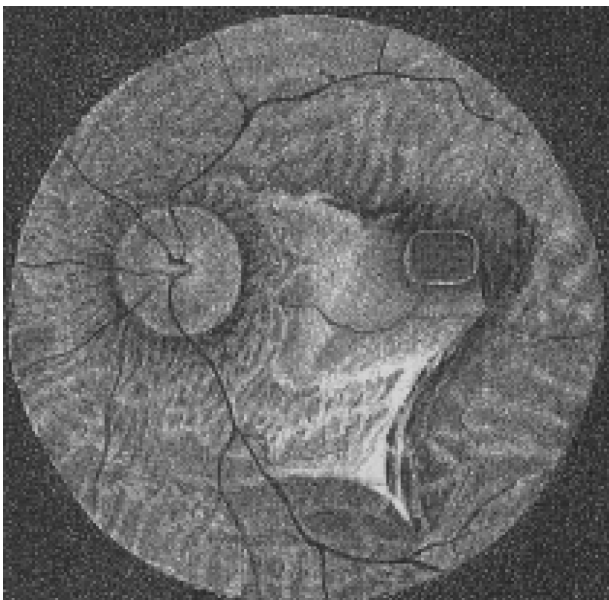
### Terminology Over the Last Decades

The terminology of AMD showed fewer variations after 1965 (Table 3). Ophthalmologists gradually became aware that *senile MD* is not a diagnosis that patients are eager to hear, quite apart from its visual implications. *Age-determined* as a substitute for *senile* was first used in Germany<sup>66</sup> and later *age-related* appeared in the American literature.<sup>67</sup> Table 3 lists a gradual change after 1965 from *senile maculopathy* and *age-related MD* to *age-related macular disease*, *ageing macula disease*, *ageing macula disorder*, and the latest term being *autoimmune macular disorder*.<sup>68</sup> All these terms share the common abbreviation AMD. The terms early and late AMD were coined around 1995.<sup>69</sup> Early AMD indicates that drusen with pigmentary changes in the macula are present in persons with the age of  $\geq 50$  years and usually it produces few visual symptoms. Late AMD is often associated with visual loss and is divided into dry late AMD, similar to geographic atrophy, and wet or neovascular AMD due to fluid leakage or hemorrhages from (new) blood vessels in the macular area.

We have achieved much since Donders, Nagel, Hutchinson, and Haab published their pioneering articles but still do not really know the cause of drusen or of AMD. I hope that this overview will place various historical concepts in proper perspective and stimulate young researchers to tie the loose ends still attached to AMD. This association was already described in 1875<sup>42</sup> and only 120 years later vascular endothelial growth factor became associated with AMD.<sup>91</sup>

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**Figure 5.** According to Junius and Kuhnt, the first drawing of disciform macular disease as seen in the eye by low magnification after removal of the anterior segment. It was called Choroido-retinitis in the region of the macula lutea. "Between the papilla and macula lutea is a whitish tract which extends downwards, becoming whiter, and terminates in a sharp point." This atlas was published in English and German.<sup>49</sup>



Heidelberg, Germany, for permission to re-use the other figures. Part of this manuscript appeared in *Historia Ophthalmologica Internationalis*. This study was partly presented at the 28th meeting of the Julius Hirschberg Gesellschaft, Bonn, Germany, October 4, 2014, and partly at the joint Cogan–Hirschberg Society meeting, New York, USA, March 28, 2015. All references may be obtained from the author unless protected by copyright or library regulations.

### Author Contributions

P.T.V.M. de Jong collected and read all literature as given in the references, wrote the first and subsequent drafts of the manuscript, thus agrees with its contents and conclusions, made critical revisions, and approved of the final manuscript.

### Abbreviations

AMD: age-related macular degeneration, age-related macular disease, ageing macula disease, aging macula disorder, autoimmune macular disease

dMD: disciform macular degeneration, disciform macular disorder

MD: macular degeneration, macular disease, macular disorder

RPE: retinal pigment epithelium.

### REFERENCES

- De Jong PTVM. From where does “rete” in retina originate? *Graefes Arch Clin Exp Ophthalmol*. 2014;252(10):1525–7.
- Magnus H. *Die Augenheilkunde der Alten* [Ophthalmology of the Ancients]. Breslau: Kern, J.U.; 1901.
- Ruysch F. *Thesaurus Anatomicus Secundus* [Second Anatomical Hoard]. Amsterdam: Waesbergen, J.; 1722.
- Eschricht DF. *Beobachtungen an dem Seebundsaug*. Observations on the seal eye. *Archiv für Anatomie Physiologie und wissenschaftliche Medicin*. 1838;575–99.
- Hovius J. *Dissertatio medico-anatomica inauguralis de circulari humorum ocularium motu* [Medical Anatomical Inaugural Thesis on the Circular Movements of the Ocular Fluids]. Utrecht: Van de Water, G.; 1702.
- De Jong PTVM. Elusive ageing macula disorder (AMD). *Hist Ophthalm Intern*. 2015;1:139–52.
- Hirschberg J. *Die Anatomie des Auges bei den alten Griechen*. [The Anatomy of the Eye with the Ancient Greeks]. *Graefe-Saemisch Handbuch der gesamten Augenheilkunde*. Leipzig: Engelmann; 1899.
- Polyak SL. *The Retina*. Chicago: The University of Chicago Press; 1941:1941.
- Platter F. *De corporis humani structura et usu* [On the Structure and Function of the Human Body]. Basel: Froben, J.; 1583.
- van Leeuwenhoek A. Letter 13. *Phil Trans R Soc*. 1674;10:378–80.
- Treviranus GR. *Resultate neuer Untersuchungen über die Theorie des Sehens und über den innern Bau der Netzhaut des Auges* [Results of New Research on the Theory of Vision and on the Internal Structure of the Retina of the Eye]. Bremen: Heyse, J.G.; 1837.
- Kölliker A. *Zur Anatomie und Physiologie der Retina* [On the anatomy and physiology of the retina]. *Verhandlungen der Physikalisch-Medizinischen Gesellschaft zu Würzburg*. 1852;(3):316–36.
- Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*. 2002;295(5557):1070–3.
- Bruch C. *Untersuchungen zur Kenntnis des körnigen Pigments der Wirbelthiere in physiologischer und pathologischer Hinsicht* [Investigations of the Granular Pigments of Vertebrates in a Physiologic and Pathologic Sense]. Zürich: Mayer u Zeller; 1844.
- Müller H. *Anatomische Beiträge zur Ophthalmologie* [Anatomical contributions to ophthalmology]. *Archiv für Ophthalmologie*. 1856;(2):1–100.
- Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PTVM. Morphometric analysis of Bruch’s membrane, the choriocapillaris, and the choroid in aging. *Invest Ophthalmol Vis Sci*. 1994;35(6):2857–64.
- Verhoeff FH, Grossman HP. The pathogenesis of disciform degeneration of the Macula. *Trans Am Ophthalmol Soc*. 1937;35:262–94.
- Nakaizumi Y. The ultrastructure of Bruch’s membrane. 1. Human, monkey, rabbit, guinea pig, and rat eyes. *Arch Ophthalmol*. 1964;72:380–7.
- Querques G, Georges A, Ben MN, Sterkers M, Souied EH. Appearance of regressing drusen on optical coherence tomography in age-related macular degeneration. *Ophthalmology*. 2014;121(1):173–9.
- Wedl C. *Grundzüge der pathologischen Histologie* [Outlines of Pathologic Histology]. Wien: Gerold, C.; 1854.
- Donders FC. *Beiträge zur pathologischen Anatomie des Auges* [Contributions to the pathologic anatomy of the eye]. *Archiv für Ophthalmologie*. 1855;(1):106–18.
- Rudnew A. *Ueber die Entstehung der sogenannten Glaskörper der Choroides des menschlichen Auges und über das Wesen der hyalinen Degeneration der Gefäße derselben* [On the origin of the so-called vitreous bodies of the choroid in the human eye and on the essence of the hyaline degeneration of its vessels]. *Virchow Archiv*. 1871;(53):455–65.
- Rosberger S, Ach T, Best G, Cremer C, Heintzmann R, Dithmar S. High-resolution imaging of autofluorescent particles within drusen using structured illumination microscopy. *Br J Ophthalmol*. 2013;97(4):518–23.
- Mimoun G, Soubrane G, Coscas G. *Les drusen maculaires* [Macular drusen]. *J Fr d’Ophthalmol*. 1990;13:19.
- Masselon J. *Mémoires d’ophtalmoscopie. Infiltration vitreuse de la rétine et de la papille*. [Ophthalmoscopic memoirs. Glasslike infiltrations of the retina and the disc]. Paris: O. Doin; 1884.
- Mondini C. *De oculi pigmento* [On the ocular pigment]. *De Bononiensi scientiarum et artium instituto atque academia commentarii*. 1791;7:29–32.
- Mondini F. *Osservazioni sul nero pigmento dell’occhio* [Observations on the black pigment of the eye]. *Opuscoli scientifici*. 1818;2:15–26.
- Jacob A. An account of a membrane of the eye, now first described. *Phil Trans R Soc*. 1819:300–7.
- Wharton-Jones T. Notice relative to the pigmentum nigrum of the eye. *Edin Med Surg J*. 1833;40:77–83.
- Ryan SJ, Mittl RN, Maumenee AE. The disciform response: an historical perspective. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1980;215(1):1–20.
- Axenfeld T. *Retinitis externa exsudativa mit Knochenbildung im Sehfähigen Auge* [External exudative retinitis with bone formation in a seeing eye]. *Graefes Arch Clin Exp Ophthalmol*. 1915;(90):452–70.
- Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium, III. Senile disciform macular degeneration. *Am J Ophthalmol*. 1967;63:45–4.
- Lerche W. *Elektronenmikroskopische Beobachtungen über altersbedingte Veränderungen an der Bruchschen Membran des Menschen* [Electron microscopic observations on age-related changes in human Bruch’s membrane]. *Anat Gesell Verb*. 1964;(60):123–32.
- Sarks SH. The fellow eye in senile disciform degeneration. *Trans Aust Coll Ophthalmol*. 1970;2:77–82.
- Sarks SH. Ageing and degeneration in the macular region: a clinico-pathological study. *Br J Ophthalmol*. 1976;60(5):324–41.
- Buzzi F. *Nuove sperienze fatte sull’occhio umano* [New Experiments done on the human eye]. Milano: Marelli; 1782:87–95.
- Soemmering ST. *De foramine centrali limbo luteo cincto retinae humanae* [On the central hole of the human retina girded by a golden-yellow fringe]. *Commentationes societatis regiae scientiarum Göttingensis*. 1796;(13):3–13.
- Cuvier G. *Leçons d’anatomie comparée. Tome 2* [Contenant les organes des sensations. Lessons on comparative anatomy. Vol 2. Containing the Organs of Sensation]. Paris: Baudouin; 1805.
- Knox R. Inquiry into the structure and probable functions of the capsules forming the canal of Petit, and of the marsupium nigrum, or the peculiar vascular tissue traversing the vitreous humor in the eyes of birds, reptiles and fishes. *Trans R Soc Edinburg*. 1826;10:231–52.
- Gloor BP. Visual axis, blind spot, yellow spot. Controversies over almost 400 years. *An Inst Barraquer*. 2015.
- Becker O. *Die Gefäße der menschlichen Macula lutea abgebildet nach einem Injectionspräparate von Heinrich Müller* [The human macular vessels depicted according to an injection preparation of Heinrich Müller]. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1881;27:1–20.
- Hutchinson J. Symmetrical central choroido-retinal disease occurring in senile persons. *R London Ophthalmic Hosp Rec J Ophthalmic Med Surg*. 1874;(8):231–44.
- De Jong PTVM. Age-related macular degeneration. *N Engl J Med*. 2006;355(14):1474–85.
- Nagel A. *Ueber Chorioiditis areolaris und über Krystalle im Augenhintergrund* [On areolar chorioiditis and crystals in the eye fundus]. *Klin Monbl Augenheilk*. 1868;4:417–20.
- Nagel A. *Hochgradige Amblyopie, bedingt durch glashäutige Wucherungen und krystallinische Kalkablagerungen an der Innenfläche der Aderhaut* [Severe amblyopia due to growths of the glass membrane and crystalline calcium deposits on the inner surface of the choroid]. *Kl Monatsbl Augen*. 1875;13:338–51.
- Nettleship E. Central guttate chorioiditis without defect of sight; premature presbyopia. *Trans Ophth Soc UK*. 1884;4:164–5.
- Nettleship E. Central senile areolar choroidal atrophy. *Trans Ophth Soc UK*. 1884;(4):165–6.
- Goldzieher W. *Ueber die Hutchinsonsche Veränderung des Augenhintergrundes* [On the Hutchinsonian change in the eye fundus]. *Wien Med Wochenschr*. 1887;37:861–5.



49. Pagenstecher H, Gent C. *Atlas der pathologischen Anatomie des Augapfels* [Atlas of the Pathologic Anatomy of the Eye Ball]. Wiesbaden: Kreidel, C.W.; 1875.
50. Silcock AQ. Choroidal gumma. *Trans Ophth Soc UK*. 1899;(19):69–71.
51. Elschmig A. *Tumorähnliche Gewebswucherung in der Macula lutea* [Tumour-like tissue proliferation in the macula lutea]. *Klin Mbl Augenb*. 1919;62:145–54.
52. Haab O. *Erkrankungen der Macula Lutea* [Illnesses of the macula lutea]. *Centralblatt für praktische Augenheilkunde*. 1885;(9):383–4.
53. Haab O, ed. *Ueber die Erkrankung der Macula lutea* [On the illness of the macula lutea]; 1888.
54. Haab O. *Atlas und Grundriss der Ophthalmoskopie und ophthalmoskopischen Diagnostik* [Atlas and Outline of Ophthalmoscopy and Ophthalmoscopic Diagnostics]. München: Lehmann; 1895.
55. Fuchs E. *Retinitis circinata* [Circinate retinitis]. *Graefes Arch Clin Exp Ophthalmol*. 1893;(39):229–79.
56. Duke-Elder S, Dobree JH. Diseases of the retina. *System of Ophthalmology*. London: Kimpton; 1967.
57. Goldzieher W. *Die Hutchinson'sche Veränderung des Augenhintergrundes (Retinitis circinata Fuchs)* [The Hutchinsonian change in the eye fundus (Fuchs' circinate retinitis)]. *Archiv f Augenheilkunde*. 1897;34:112–34.
58. Van der Hoeve J. *Retinitis exsudativa* [Exudative retinitis]. *Ned Tijdschr Geneesk*. 1915;59:1637–40.
59. Batten R. Peculiar symmetrical swellings in the macular region, apparently due to subretinal haemorrhage. *Trans Ophth Soc UK*. 1904;24:127.
60. Possek R. *Ueber senile Maculaveränderung bei Arteriosclerose* [On senile macular change in arteriosclerosis]. *Z Augenheilkunde*. 1905;(13):771–9.
61. Coppez H, Danis M. *Rétinite exsudative maculaire sénile* [Senile exudative macular retinitis]. *Arch Ophthalmol*. 1923;40:129–54.
62. Oeller J. *Atlas der Ophthalmoskopie* [Atlas of Ophthalmoscopy]. Wiesbaden: Bergmann, J.F; 1896–9.
63. Junius P, Kuhnt H. *Die scheibenförmige Entartung der Netzhautmitte. Degeneratio maculae luteae disciformis* [The Disciform Degeneration of the Central Retina. Disciform Macula Lutea Degeneration]. Berlin: Karger, S.; 1926.
64. Duke-Elder S, Perkins ES. *System of Ophthalmology*. London: Kimpton; 1966.
65. Duke-Elder S, Dobree JH. Diseases of the retina. Degenerations and dystrophies. *System of Ophthalmology*. London: Kimpton, H; 1967.
66. Straub W. *Altersbedingte Maculadegeneration* [Age-determined macular degeneration]. *Dtsch Med Wochenschr*. 1969;94:1385–6.
67. Sunness JS. Age-related macular degeneration: how science is improving clinical care. Interview by Marc E. Weksler. *Geriatrics*. 1998;53(2):70–80.
68. Camelo S. Potential sources and roles of adaptive immunity in age-related macular degeneration: shall we rename AMD into autoimmune macular disease? *Autoimmune Dis*. 2014.
69. Bird AC. Age-related macular disease: aetiology and clinical management. *Community Eye Health*. 1999;12(29):8–9.
70. Oeller J. *Atlas seltener ophthalmoskopischer Befunde* [Atlas of Rare Ophthalmoscopic Findings]. Wiesbaden: Bergmann, J.F; 1904.
71. Michel J. *Ueber Geschwülste des Uvealtractus* [On tumours of the uveal tract]. *Graefes Arch Clin Exp Ophthalmol*. 1878;(34):131–47.
72. Caspar L. *Ein Fall von seniler Degeneration in der Gegend der macula lutea* [A case of senile degeneration in the region of the macula lutea]. *Klin Monatsbl Augenheilk*. 1892;30:284–7.
73. Walker CH. A case of new growth in the macular region. *Trans Ophth Soc UK*. 1897;(17):64–5.
74. Yarr MT. Central choroido-retinitis, resembling an optic disc, in a patient suffering from glycosuria. *Trans Ophth Soc UK*. 1899;(19):68–9.
75. Jessop WH. Tumour in region of yellow spot. *Trans Ophth Soc UK*. 1903;(23):384–6.
76. Lawford JB. A case of subretinal new growth of doubtful nature. *Trans Ophth Soc UK*. 1911;31:257–60.
77. Mosso G. *Degenerazione disciforme della macula. Anastomosi arterio-venosa* [Disciform degeneration of the macula. Arterio-venous anastomoses]. *Annali di Ottalmologia*. 1912;41:325–37.
78. Heinricy O, Harms C. *Klinische Beiträge zur Degeneratio circinata retinae (Retinitis circinata (Fuchs)) mit besonderer Berücksichtigung der atypischen Formen des Krankheitsbildes* [Clinical contributions to circinate degeneration of the retina [Fuchs'circinate retinitis] with special emphasis on the atypical forms of the clinical picture]. *Graefes Arch Clin Exp Ophthalmol*. 1913;86:514–48.
79. Hegner CA. *Retinitis exsudativa bei Lymphogranulomatosis* [Exudative retinitis in lymphogranulomatosis]. *Klin Monbl Augenb*. 1916;57:27–48.
80. Nöthen H. *Ueber Vortäuschung von Tumoren in der Maculagegend durch Retinitis exsudativa haemorrhagica Coats* [On Simulation of Tumors in the Macular Area by Coats' Exudative Hemorrhagic Retinitis]. Bonn: Trapp, H; 1920.
81. Salzmann M. *Fuchs Lehrbuch der Augenheilkunde* [Fuchs' Textbook of Ophthalmology]. 15th ed. Leipzig: Deuticke; 1926.
82. Laird RG. Iodide Therapy for senile macular degeneration. *Trans Am Ophthalmol Soc*. 1944;42:480–94.
83. Maumenee AE. Serous and hemorrhagic disciform detachment of the macula. *Trans Pac Coast Otoophthalmol Soc*. 1959;40:139–69.
84. Wessing A. *Die exsudative senile Makulopathie, klinisches Bild, Pathogenese, prognose und Therapie* [The exudative senile maculopathy, clinical picture, pathogenesis, prognosis and therapy]. *Klin Mbl Augenheilk*. 1977;171:371–84.
85. Folk JC. Aging macular degeneration. Clinical features of treatable disease. *Ophthalmology*. 1985;92(5):594–602.
86. Klein R, Meuer SM, Moss SE, Klein BEK. Detection of drusen and early signs of age-related maculopathy using a nonmydriatic camera and a standard fundus camera. *Ophthalmology*. 1992;99:1686–92.
87. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol*. 1995;39(5):367–74.
88. Holz FG, Wolfensberger TI, Piguet B, Minassian D, Bird AC. *Makuläre Drusen* [Macular drusen]. *Ophthalmologie*. 1994;91:735–40.
89. Pagliarini S, Moramarco A, Wormald RP, et al. Age-related macular disease in rural southern Italy. *Arch Ophthalmol*. 1997;115(5):616–22.
90. De Jong PTVM, Lubsen J. The standard gamble between cataract extraction and AMD. *Graefes Arch Clin Exp Ophthalmol*. 2004;242(2):103–5.
91. Kliffen M, Sharma HS, Mooy CM, Kerkvliet S, de Jong PTVM. Increased expression of angiogenic growth factors in age-related maculopathy. *Br J Ophthalmol*. 1997;81:154–62.