



Elusive drusen and changing terminology of AMD

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Abstract

The first descriptions of ageing macula disorder (AMD), be it under other names, appeared in 1855 and 1868. The earliest accounts of AMD linked the presence of drusen with visual loss. It took a century before these connections between drusen and AMD were generally accepted by medical science and in clinical articles. The first signs of AMD appear in the region of the choriocapillaris, Bruch's membrane and the retinal pigment epithelium. The pathogenesis of drusen and of AMD is still uncertain. This is reflected in the wide variation in nomenclature of both, since the first publications.

Introduction

Our knowledge of ageing macula disorder (AMD) has markedly increased over the last 50 years in tandem with a growing interest in this disorder, partly owing to its increased prevalence in populations with a higher life expectancy. Later in this review, an explanation is given as to why the term ageing macula disorder is preferred to age-related macular degeneration (both similar, and abbreviated as AMD), a disorder that by definition occurs only in persons arbitrarily 50 years of age or older [1]. The first aim of this review is to examine, where possible, the earliest available descriptions of tissue changes that are at the present time considered to be associated with AMD, among others of drusen. There are reviews on the pathogenesis or treatment of AMD but these did not focus on changes in its nomenclature [2–4]. The first publications indicating AMD spring from 160 years ago. Changes in AMD terminology since the first publications will be discussed, revealing the uncertainty of researchers about the pathophysiology of AMD.

Original descriptions of tissue changes associated with AMD from the outer to the inner eye

The choroid

The choroid is customary divided into the large vessel layer of Haller, the smaller vessel layer of Sattler, and the choriocapillaris. Duke–Elder considered Bruch's membrane (BrM) to be part of the choroid [5]. With advancing age the choroid, including the choriocapillaris, becomes thinner in maculae with or without signs of AMD. In neonates its thickness is 0.15–0.3 mm, in adults 0.1 mm [6]. In very old people the reduction in choroidal thickness is 57% compared with the youngest age group [7]. The choroid in AMD was reported to be either normal or have sclerotic vessels with atheromatous changes. The choriocapillaris was considered by some to be the primary affected tissue and in it lymphocytes were found near AMD lesions [2].

Bruch's membrane (BrM)

Carl Bruch described this membrane, which was named after him, in 1844 in his monograph on granular pigments in vertebrates [8]. BrM is an extracellular matrix between the choriocapillaris and the retinal pigment epithelium (RPE). Bruch wrote that Eschricht described six years earlier this membrane in the seal [8]. Thus BrM should have been called Eschricht's membrane [9]. Early researchers noticed that BrM becomes thicker around age 70 years [10]. It thickens over time by 135% whether signs of AMD are present or not [7]. Histologically, half of 13 eyes

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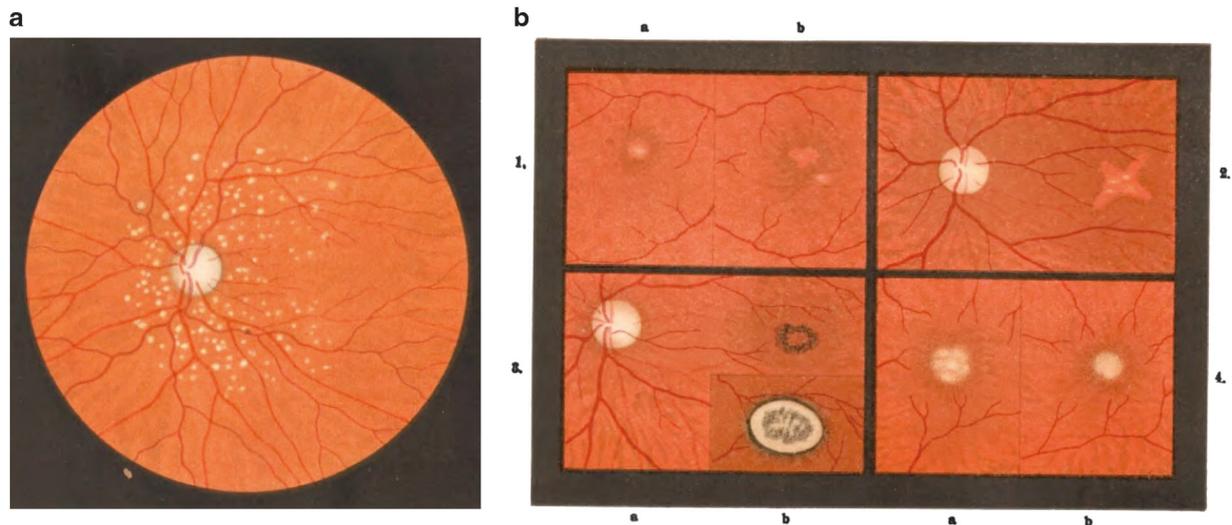


Fig. 1 (a) Drusen of the vitreous membrane of the choroid. Haab wrote: These drusen, also a change in old age, have nothing to do with the macular disorder depicted here and should be distinctly separated from this. [20] (b) Images of senile macular disease. [20] 1. a b Macula

of right and left eye from a 70-year-old person; 2. No legend given. 3. a Beginning signs of disease; b 6 months later; 4. a b Right and left eye from a 74-year-old female

with disciform macular degeneration (dMD) had ruptures in BrM which were crossed by new vessels [2]. So for ~80 years people knew that changes in BrM were associated with AMD. Only recently, three types of multilaminar sub-RPE hyper reflectivity were detected with optical coherence tomography in the inner, the outer, or both layers of BrM, in eyes with regressing drusen [11].

The retinal pigment epithelium (RPE)

The retinal pigment epithelium was first described in 1791 [12, 13]. Bruch again elaborately described the RPE and was struck by its monolayer and regular, hexagonal shape [8]. 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 [8]. Frans Donders mentioned in 1855 RPE atrophy between groups of drusen [14]. It gradually became clear that the RPE could become hypertrophied and after fibrous metaplasia could contribute to fibrous tissue in disciform lesions [2, 3, 15, 16].

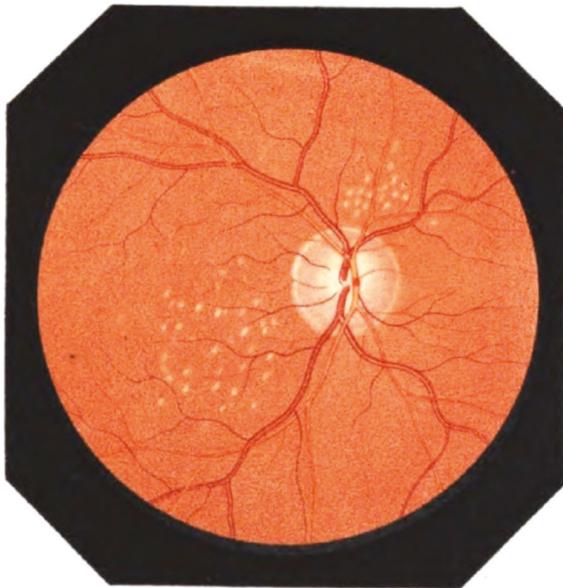
Basal laminar or basal linear deposits between the cell membrane and the basement membrane of the RPE, are often present before drusen appear. These terms were not used in the original electron microscopic descriptions of these deposits [17]. Don Gass called them 'eosinophilic material between an irregularly thickened BrM and overlying degenerated RPE' [16]. Shortly afterwards Shirley Sarks identified in 1970 three types of deposits [18] and it seems that she coined the term basal linear deposit [19].

Drusen

Drusen are small yellow–white deposits on BrM that press while enlarging through the RPE and thus become visible on ophthalmoscopy as white spots in the retina, both in the macular area as in the retinal periphery. Drusen are now considered to be a hallmark of AMD but this connection was explicitly denied by Haab who first described senile Macular Disease (MD) (Fig. 1) [20]. Around 1850, three authors, Wedl, Donders, and Müller, gave drusen different labels (Table 1). Carl Wedl named them colloid bodies of the choroid and thought they were incompletely developed cells, because they had no cell membrane or nucleus [21]. Donders called them colloid balls surrounded by pigment, noting their preference for the macular area. He used ~10 acids and lye's at various temperatures, even boiling them to determine their composition, thus being one of the first ophthalmic histochemists. He described the growth and confluence of the drusen and concluded that drusen originate from RPE cell nuclei [14]. Heinrich Müller mentioned deposits on the inner side of the choroid that had a ball-shaped or drusenoid form. In this paper from 1856 he coined the word 'druse' (Table 1) [10]. 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 [22]. The first color image of drusen appeared in 1869 (Fig. 2) [23]. Over the years, several subtypes of drusen were discovered, one of the latest subdivisions being reticular, cuticular, or pseudodrusen [24]. Müller wrote that drusen originate behind the RPE and arise from focal thickenings in the structureless layer on the inner side of the choroid [10]. Later, the theory was

Table 1 Various names for drusen

Year	Author	Original name	English translation
1854	Wedl [21]	Colloidkörper von der Chorioidea	Colloid bodies of the choroid
1855	Donders [14]	Colloidkugeln	Colloid balls
1856	Müller [10]	kugelig-drusigen Körper; Druse	Ball-shaped, drusenoid bodies; druse
1868	Nagel [40]	Krystalle; Krystalldrusen	Crystals; crystal drusen
1869	Jäger von Jaxtthal [23]	Knotenförmige Exsudate in der Gefäßshaut	Nodular exudates in the choroid
1874	Hutchinson [36]		'Colloid' excrescences from the lamina elastica
1875	Nagel [68]	Glashäutige Wucherungen	Proliferations of the glass membrane
1884	Masselon [27]	Excroissances verruqueuses de la choroïde	Warty growths of the choroid
1896	Oeller [70]	Verrucae laminae vitreae	Warts of the glass membrane

**Fig. 2** First color image of drusen. These were called: Nodular exudates in the choroid. Table 1 [23]

formulated that drusen originate from leukocytes [25]. 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, as Donders suggested [14, 26]. In 1884 drusen were even considered to be the cause of 'postérieur' glaucoma because drusen usually were located around the optic disc. This led to the assumption that thickening of the glasslike layer around the choroidal ring hampered the outflow of ocular fluid. This view was supported by the fact that drusen as well as glaucoma normally were present in both eyes of old persons (Fig. 3) [27].

The retina

The word retina was coined around 1150 AD by Gerardus Cremonensis in a mediaeval Latin translation of an Arabic text [28]. Felix Platter indicated in 1583 that the retina and not

the lens was the light-sensitive organ in the eye [29]. Nearly 100 years later, a discoverer of the microscope, Antony van Leeuwenhoek, referred to 'cloodgens' at the end of the fibers of the optic nerve spreading in the eye, that transmitted visible objects to the brain [30]. He used in Dutch the word 'cloodgens' both to indicate cells and fat globules. The English translation of 'cloodgens' as simply 'globules' may have blurred this distinction [30]. The photoreceptors were rediscovered 150 years later [31]. In 1839 Bidder depicted rods and cones in the chicken and mentioned that the rods were not oriented toward the light (the cornea) but towards the RPE [32]. Albert Kölliker was the first to describe the rods and cones in the human eye as two types of photoreceptors [33]. Only recently, new photosensitive ganglion cells were discovered in the retina, which drive the circadian clock via the suprachiasmatic nucleus [34].

In 1782, Francesco Buzzi described the retinal center, the macula lutea, after dissecting the eyes of a 35-year-old man [35]. The pathogenetic process underlying AMD is still not clear, nor 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 ruptures in BrM and RPE detachments leading to subretinal hemorrhages precede retinal changes of a secondary nature like photoreceptor loss or scarring [2, 36]. It took nearly another 125 years since the paper by Verhoeff before angiogenic growth factors were discovered in AMD [37].

Early reports on AMD

As a lecturer in physiology, Donders hardly earned enough money to support his family. He agreed to translate Ruete's Textbook of Ophthalmology from German in Dutch while moonlighting, and thus became interested in ophthalmology. Two years after the invention of the ophthalmoscope [38] Donders' PhD student Adrien van Trigt wrote in 1853 a thesis on ophthalmoscopy in which the first world-wide color images of the fundus appeared (Fig. 4) [39]. In his early medical career Donders performed many autopsies.

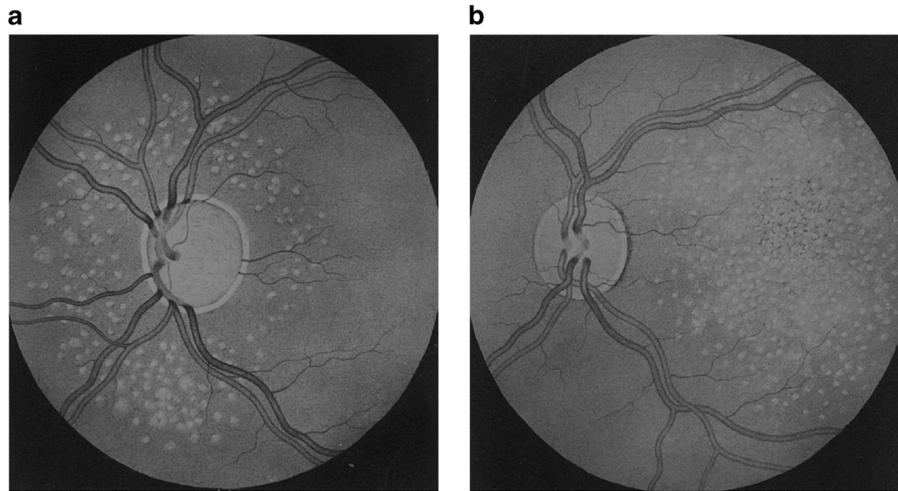


Fig. 3 (a) Inferred association between 'posterior' glaucoma with total disc cupping and circumpapillary drusen. [27] (b) Drusen and pigmentary changes in the fundus

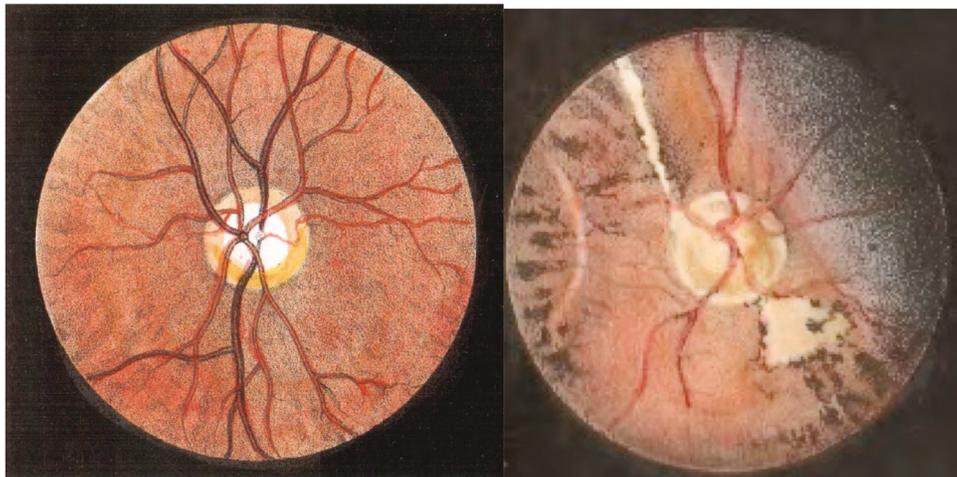


Fig. 4 First color images ever of the eye fundus [39] from thesis by Van Trigt [67]

From 1852 on, he realized the gap in understanding between what he saw using the ophthalmoscope and the microscope. So he started collecting 'healthy' post mortem 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' [14]. Using microscopy he noticed rods, obliquely oriented around small drusen as well as degeneration of the choriocapillaris and the RPE. On the choroidal side of the retina, 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. 5) and rarely were absent in the eyes of persons aged 70–80 years. In none of the eyes that Donders examined post mortem, had the visual acuity 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 the retinal function. He concluded that it would be rash to predict what these colloid changes would look like using ophthalmoscopy. Donders was convinced that the white flecks that he had seen several times 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 [14]. An enviable clinical insight.

Albrecht Nagel was probably the first to publish on AMD, using both clinical and histological data from the same patient. 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', increasing metamorphopsia, and a quivering image [40]. Fine brilliant specks were present, creating the impression of 'Krystalldrusen'. Nagel published again on this woman

and some more cases with AMD [41]. The visual fields of these patients were normal and the eyes were never painful or inflamed. His first patient died at age 73 owing to an abdominal tumor; the eyes were enucleated 27 h post mortem and one was put in Müllers fixative. In the non-fixated eye, there were small, sparkling irregularities in the posterior pole on the inner side of the choroid. They contained hard grains with a diameter up to 0.5 mm that crunched under the tip of a knife. They were markedly similar to the whitish crystal-like drusen seen on ophthalmoscopy. Nagel concluded that the crystalline mass consisted of carbonic acid lime. On microscopy, lighter round flecks, surrounded by a black pigment ring were seen in the RPE. The flecks were created by thickenings of the elastic layer where the drusen, who were in the meantime dissolved in the fixative, 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.

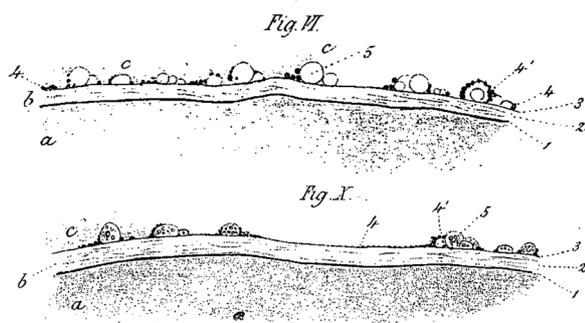


Fig. 5 Large drusen (5) pressing against the retina (c) [14]. aa is choroid, b probably Bruch's membrane, c retina in which drusen protrude

Terminology of AMD from 1855 onwards

Table 2 lists the huge variety of terms that 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 the pathophysiologic concept they indicate, will be commented on. In 1874, Jonathan Hutchinson described a choroid, 'speckled with minute dots of yellowish white deposits' [36]. 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, whereas the great defect of sight which accompanies it points to implication of the retina secondarily'. He formulated three stages in the disease: 1. Scattered yellow-white spots; 2. Coalescence of these to patches with irregular borders; 3. Hemorrhage at the yellow spot and absorption of the blood. Essentially, he thus had already described the present-day paradigm of the clinical course from drusen to late AMD. Nettleship mentioned in 1884 central guttate choroiditis, with a plate that clearly showed drusen, what we now would name early AMD (Fig. 6a) [42]. He also published in the same year on central senile areolar choroidal atrophy, probably now called dry late AMD (Fig. 6b) [43]. Soon afterwards, AMD was referred to as 'Hutchinsonian changes of the posterior pole of the eye' [44]. Wilhelm 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, nor colloid excrescences of the vitreous membrane of the choroid, but compared them with cerebral leukomalacia caused by occlusions of the macular arterioles [44]. In subsequent years, diagnoses such as chorioretinitis [45], syphilis [46], or tumors [47–50] most likely were referring to AMD.

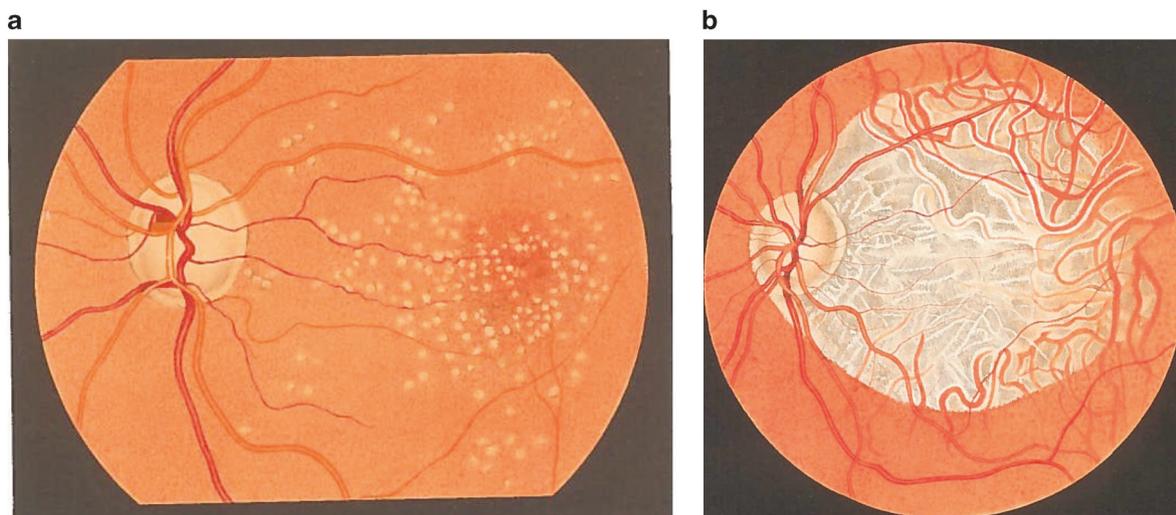


Fig. 6 (a) Central guttate choroiditis [42] (b) Central senile areolar choroidal atrophy [43]

Table 2 Terminology of ageing macula disorder (AMD) from its very beginning^a

Year	Author	Original terminology	English (translation)
1855	Donders [14]	Entartung der Choriocapillaris und der Pigmentschicht; Amblyopia senilis	Degeneration of the choriocapillaris and the pigment layer; senile amblyopia
1868	Nagel [40]	Über chorioiditis areolaris und über Krystalle im Augenhintergrunde	On areolar choroiditis and on crystals in the ocular background
1874	Hutchinson [36]		Symmetrical central choroido-retinal disease occurring in senile persons; Tay's central guttate choroiditis [49]
1875	Nagel [68]	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 [45]	Chorioido-Retinitis in Regione Maculae Luteae;	Chorioretinitis in the region of the macula lutea
1878	Michel [47]	Ueber Geschwülste des Uvealtractus	On tumors of the uveal tract
1884	Nettleship [43]		Central senile areolar choroidal atrophy
1884	Nettleship [42]		Central guttate choroiditis
1884	Masselon [27]	Infiltration vitré de la rétine	Glasslike retinal infiltration
1885	Haab [51]	Erkrankungen der Macula Lutea; senile Maculaerkrankung;	Diseases of the macula lutea; Senile macular disease
1887	Goldzieher [44]	Ueber die Hutchingsonse Veränderung des Augenhintergrundes	On Hutchinsonian changes in the posterior pole of the eye
1892	Caspar [68]	Senile Degeneration in der Gegend der macula lutea	Senile degeneration in the region of the macula lutea
1893	Oeller [69]	Chorio-Retinitis centralis. Anastomosis arterio-venosa;	Central chorioretinitis. Arteriovenous anastomosis
1893	Fuchs [53]	Retinitis circinata	Circinate retinitis
1897	Walker [48]		New growth in the macular region
1899	Silcock [46]		Choroidal gumma
1899	Yarr [70]		Central choroido-retinitis resembling an optic disc
1903	Jessop [49]		Tumor in region of yellow spot
1903	Oeller [60]	Degeneratio maculae luteae disciformis;	Disciform macular degeneration
1904	Batten [57]		Peculiar symmetrical swellings in the macular region
1905	Possek [58]	Senile Maculaveränderung bei Arteriosklerose;	Senile macular change in arteriosclerosis
1911	Lawford [72]		Subretinal new growth of doubtful nature
1912	Mosso [73]	Degenerazione disziforme della Macula;	Disciform degeneration of the macula
1913	Heinrici [74]	Degeneratio circinata retinae (Ret. circinata Fuchs)	Retinal circinate degeneration (Fuchs' circinate retinitis)
1915	Axenfeld [15]	Retinitis externa exsudativa	External exudative retinitis
1915	Van der Hoeve [56]	Retinitis exsudativa externa	External exudative retinitis
1916	Hegner [75]	Retinitis exsudativa	Exudative retinitis
1919	Elschnig [50]	Tumorähnliche Gewebswucherung in der Macula lutea;	Tumor-like tissue proliferation in the macula lutea
1920	Nöthen H [76]	Tumoren in der Maculagegend; Retinitis exsudativa haemorrhagica Coats;	Tumors in the macular region; exudative hemorrhagic retinitis of Coats
1923	Coppez H [59]	Rétinite exsudative maculaire sénile	Senile exudative macular retinitis
1926	Junius, Kuhnt [61]	Die scheibenförmige Entartung der Netzhautmitte (Degeneratio maculae luteae disciformis). Scheibenförmige Erkrankung der Netzhautmitte	Disciform degeneration of the retinal center (Disciform macular degeneration). Disciform disease of the retinal center
1926	Fuchs' Salzmann [22]	Senile Makuladegeneration; zentrale senile Retinochoroiditis	Senile macular degeneration; central senile chorioretinitis

Table 2 (continued)

Year	Author	Original terminology	English (translation)
1937	Verhoeff [2]		Senile disciform degeneration of the macula
1944	Laird [77]		Senile macular degeneration
1959	Maumenee [78]		Serous and hemorrhagic disciform detachment of the macula
1966	Duke-Elder [62]		Senile macular degeneration; Senile macular chorioretinal degeneration; Senile macular degeneration of Haab; Senile disciform degeneration of the macula of Junius and Kuhnt
1967	Gass [16]		Disciform detachment of the neuroepithelium; Senile disciform macular detachment; Senile macular degeneration; Senile macular choroidal degeneration
1969	Straub [63]	Altersbedingte Maculadegeneration;	Age-determined macular degeneration
1977	Wessing [79]	Exsudatieve senile Makulopathie	Exudative senile maculopathy
1985	Folk [80]		Aging macular degeneration
1987	Sunness [64]		Age-related macular degeneration
1992	Klein [81]		Age-related maculopathy
1996	Holz [82]	Altersabhängige Makuladegeneration	Age-dependent macular degeneration
1997	Pagliarini [83]		Age-related macular disease
2004	De Jong [83]		Ageing macular disease
2006	De Jong [4]		Aging macula disorder
2014	Camelo [65]		Autoimmune macular disease

^a Only the first time a certain concept was encountered is given here, unless for different [65] (historical) reasons

Although Edward Nettleship had already mentioned central senile areolar choroidal atrophy [43], Otto Haab was the first to report 1 year later in 1885 on 'Senile Makulaerkrankung', (senile macular disease) as a separate entity among the MDs, starting in the RPE (Fig. 1b) [20, 51, 52]. No other articles by Haab have come to light, explaining why he decided that senile MD was a separate entity. He concluded from analyzing over 50 000 patient files that senile MD was about as frequent as traumatic MD and myopic macular affection. Senile MD was often bilateral and 'one should be wary of the outcome of a mature cataract operation when the fellow eye had this MD' [52]. It is striking that Haab explicitly stated that drusen, 'quite innocent changes in old persons', had nothing to do with senile MD (Fig. 1a) [20].

An article in 1893 by Fuchs on circinate retinitis, a circle of white flecks around the fovea [53], precipitated an avalanche of over 50 papers on this topic [54–56]. Circinate degeneration [55], or senile exudative retinitis were proposed as more precise terms [56]. A review on 61 out of 129 eyes with dMD having white spots, showed that 36% had circinate retinitis [2]. In 1904, 30 years after Hutchinson's paper, subretinal hemorrhages in AMD came again to the attention of researchers [57] and 1 year later atherosclerosis was suggested as a possible cause [58]. 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 [59].

In the legend which accompanies the image of the eye of a 79-year-old man from Johann Oeller's atlas (Fig. 7), the word 'disciform' appears to have been used for the first time [60]. The first image of disciform macular disease (dMD) was probably image number 6 in Hermann Pagenstecher's atlas called 'Choroido-Retinitis in the region of the macula lutea' [45, 61]. The breakthrough in relation to 'disciform' MD, however, was the classic monograph by Paul Junius and his predecessor Hermann Kuhnt [61]. 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 'disease' of the retinal center, one 'degeneration' of this center, and eight cases received both. 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 disciform disorders varied from alcoholism and lues to hypertension and atherosclerosis. This monograph is valuable for the following three reasons: first, the excellent overview of the



Fig. 7 Disciform macular degeneration. Male, 79 years old. Round center, over 2.5 diopter prominence [60]

past literature on dMD; second, the detailed color drawings; and, finally, it informed the wider public about dMD [61]. In the epilogue on page 132 was written: 'The expression disciform disease 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' (disease) to 'Entartung', (degeneration) in order to attract attention? [61] 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. Junius and Kuhnt could not help the fact that for many years their names were coupled to AMD. This was partly because Verhoeff [2] and later Duke-Elder [62] added to the original title of their monograph the word 'senile' or started a sub-chapter with: 'Senile disciform degeneration of the macula (*of Junius and Kuhnt*)'. The limited knowledge 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 macula disease!) or Senile Macular Degeneration' [62]. Drusen were dealt with in a few pages under the sub-category 'Secondary degenerations' [54].

Ageing macula disorder

Terminology showed fewer variations after 1965. Ophthalmologists gradually became aware that 'senile' MD is not a diagnosis patients are eager to hear, quite apart from

its visual implications. 'Age-determined' as a substitute for 'senile' was first used in Germany [63] and later age-related appeared in the American literature [64]. In Table 2, one may see a gradual change after 1965 from senile maculopathy and age-related MD to age-related macular disease, ageing macula disease, ageing macula disorder, the latest term being 'autoimmune macular disorder' [65] (all abbreviated as AMD).

On the eve that an article of mine [4] was due to go to the printer, I received a phone call from the editor-in-chief who wanted to change its title from Aging Macula Disorder into Age-related Macular Degeneration. We agreed to change the title but when placing my arguments for Aging Macula Disorder at the end of the article, some of their tenor was lost. In the interest of greater clarity, I will summarize my arguments here:

1. A good doctor should burden the patient with as little confusing or even alarming information as possible, especially when it has no therapeutic consequences. A few tiny drusen are not the same as late AMD. The Macular Disease Society in the UK, recently even dropped 'Disease' from its name, to the accompaniment of a huge round of applause by its members when this was announced at the annual meeting.
2. We know many types of MD, often in very specific age groups but 'age-related' does not adequately differentiate between MD in the newborn, infant [66], juvenile dMD [2], MD in the adult or in old persons.
3. Ageing macula simply signifies to me a macula in a person above a certain age, in the case of AMD commonly and arbitrarily set at age 50 [1].
4. The concept of degeneration in pathology is actually rather a vague one.

We achieved much since Donders, Nagel, Hutchinson, and Haab published their pioneering papers. 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.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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