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FUCHS' UVEITIS SYNDROME: NO LONGER A SYNDROME?

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ABSTRACT (English)

Recent reports have implicated rubella virus in the etiology of Fuchs' uveitis (FU). This review aims to present an overview of the current knowledge, mainly on the subject of rubella virus as the etiologic agent. A literature search was conducted using the PubMed database. Several characteristics appear to distinguish Fuchs' uveitis from other uveitis forms: low-grade inflammatory activity, characteristic iris atrophy, the absence of posterior synechiae, lack of response to corticosteroids and often resulting in secondary cataract and glaucoma. Fuchs' uveitis is traditionally diagnosed on clinical grounds, but is often referred to as one of the most frequent misdiagnosed uveitis types. Misconceptions about the clinical picture play an important role: Fuchs' uveitis is not exclusively an anterior uveitis and heterochromia is classically overemphasized. Recently, more attention is focused on posterior involvement: vitreous opacities and disc hyperfluorescence on fluorescein angiography. Determining internationally accepted diagnostic criteria is highly necessary in order to avoid misdiagnosis. Treatment is unnecessary for the inflammation itself but should be directed towards the complications: cataract, vitreous opacities and glaucoma. The latter, albeit less frequent, causes the most problems and should be actively screened for. Cataract extraction and vitrectomy lead to few problems and may be combined when necessary. Several etiologies have been suggested for Fuchs' uveitis, but only recently, consistent results have demonstrated an important role for rubella virus. Analysis of the results of anti-rubella antibody detection in the aqueous strongly supports this association. The way rubella virus is contracted is still in doubt: both acquired and congenital rubella are possible, vaccination as a cause is very doubtful. The atypical course of Fuchs' uveitis and its mainly unilateral nature remain difficult to explain. Diagnosis of Fuchs' uveitis can be confirmed using laboratory testing but this requires an anterior chamber tap. Indications for diagnostic paracentesis still need to be determined. No treatment is able to influence the natural course of Fuchs' uveitis and the knowledge that the disease is due to rubella virus will not alter this fact. Since rubella vaccination causes a decrease in the prevalence of Fuchs' uveitis, it could be used as a preventive measure against the development of this condition. The recent, convincing findings on the etiology indicate that the term Fuchs' uveitis syndrome should no longer be used: it should be classified as a disease rather than as a syndrome.

ABSTRACT (Nederlands)

Recente artikels hebben het rubellavirus gelinkt aan de etiologie van Fuchs' uveïtis (FU). Deze review heeft als betrachting een overzicht te bieden omtrent de huidige kennis over de ziekte, met de focus op de rol van het rubellavirus als etiologisch agens. Een literatuuronderzoek werd hiervoor uitgevoerd via de PubMed database. Fuchs' uveïtis blijkt zich op basis van verschillende karakteristieken te onderscheiden van andere vormen van uveïtis: een laaggradige inflammatoire activiteit, karakteristieke irisatrofie, afwezigheid van posterieure synechieën, gebrekkige respons aan corticosteroïdtherapie en vaak resulterend in secundair cataract en glaucoom. De diagnose van Fuchs' uveïtis wordt klassiek op klinische basis gesteld, maar het wordt frequent genoemd als een van de vaakst foutief gediagnosticeerde types van uveïtis. Incorrecte opvattingen omtrent het klinisch beeld spelen hierbij een belangrijke rol: Fuchs' uveïtis is niet louter een anterieure uveïtis en de nadruk ligt traditioneel te sterk op heterochromie. Recent is de focus veeleer gericht op de posterieure aantasting, voornamelijk de vitreale opaciteiten en discus hyperfluorescentie op fluoresceïne angiografie. Het bepalen van internationaal aanvaarde diagnostische criteria dringt zich op in het kader van het vermijden van foutieve diagnostiek. Behandeling is onnodig voor de ontsteking zelf, maar dient gericht worden op de complicaties: cataract, vitreale opaciteiten en glaucoom. Dit laatste, zij het minder frequent, zorgt voor de meeste problemen. Actieve screening naar glaucoom bij patiënten met Fuchs' uveïtis is dan ook aangewezen. Cataractextractie en vitrectomie zorgen voor weinig problemen en kunnen indien nodig gecombineerd worden. Verscheidene etiologieën zijn in het verleden gesuggereerd voor Fuchs' uveïtis, maar het is slechts sinds kort dat consistente resultaten wijzen op een belangrijke rol voor het rubellavirus. Een analyse van de resultaten van anti-rubella antilichaamdetectie in het kamervocht biedt een krachtige ondersteuning van dit verband. Hoe de infectie met het rubellavirus precies opgelopen wordt, is nog steeds twijfelachtig: zowel een verworven als een congenital rubella-infectie zijn mogelijk, vaccinatie als een oorzaak van Fuchs' uveïtis valt sterk te betwijfelen. Het atypische verloop van Fuchs' uveïtis en het voornamelijk unilateraal karakter blijven moeilijk te verklaren. De diagnose van Fuchs' uveïtis kan op betrouwbare wijze bevestigd worden via een laboratoriumtest. Dit vergt echter een kamervocht analyse. Exacte indicaties voor een diagnostische paracentese dienen nog bepaald te worden. Geen enkel type behandeling is in staat het natuurlijk verloop van Fuchs' uveïtis te beïnvloeden en de kennis dat de aandoening veroorzaakt wordt door het rubellavirus zal dit feit niet veranderen. Aangezien rubella vaccinatie een afname van de prevalentie van Fuchs' uveïtis teweegbrengt, kan dit gebruikt worden als preventieve maatregel om de ontwikkeling van de aandoening tegen te gaan. De recente, overtuigende bevindingen omtrent de etiologie duiden erop dat de benaming Fuchs' uveïtis syndroom niet langer dient gebruikt te worden: het moet geclassificeerd worden als een ziekte veeleer dan als een syndroom.

1. Introduction

1.1 INTRODUCTION

Fuchs' uveitis is an intriguing ocular condition, first mentioned in medical literature as early as the 19th century. This unusual and atypical form of uveitis represents roughly 2 to 3% of all uveitis cases. It is traditionally described as a low-grade, chronic uveitis that lacks manifest signs of inflammation and is often associated with heterochromia. The usually brief entry in ophthalmological textbooks appears to be quite misleading and causes underdiagnosis of this condition. Although the disease bears his name, Ernst Fuchs was not the first to describe it. Lawrence (1843) described the coincidence of cataract and heterochromia in four patients[1, 2]. Additional patients were mentioned in subsequent, concise case reports, until Fuchs' publication in 1906. Ernst Fuchs, Professor at the University of Vienna from 1885 till 1916, was an authority in ophthalmology. Next to Fuchs' uveitis, other ocular conditions were named after him: Fuchs' endothelial dystrophia, a degenerative condition of the corneal endothelium resulting in corneal edema and possible visual loss[3]. Because of his extensive, detailed study on the disease, Fuchs' uveitis also carries his name. He called it 'Zyklitis bei Heterochromie', which shows that heterochromia was perceived as a highly important part of the condition. Fuchs described the clinical features briefly in 1902 in the 9th edition of his textbook and concluded that little was known about the condition, a fact he changed himself a few years later. In this textbook, Fuchs' uveitis was part of the chapter 'Komplikationen der Heterochromie'. This illustrates the perception on the disease at that time: the paler iris was considered responsible for the other ocular manifestations, as the cause instead of the consequence. Georges Weill published an article in 1904 on 7 patients, each showing heterochromia, cataract, cyclitis and keratic precipitates[4]. Weill did not merely consider this a lack of pigment but believed that the patients showed signs of an underlying uveal condition. As such, Weill did not follow the mainstream and felt the pallor of the iris was a consequence rather than the cause of the pathological condition. Fuchs' description of the disease was based on the clinical information of 38 patients he had studied in the preceding 10 to 15 years and the histologic data of 6 iris specimens[5]. This group of patients was far larger than those of previous studies and the specimens gave Fuchs the opportunity to correlate the clinical features to the histopathological findings. This was quite remarkable, as it is not that simple to retrieve specimens for scientific purposes, because human material for research was and still is scarce[1]. Fuchs studied patients of Caucasian decent, as did many authors following him. Since most of these patients had light-coloured irides, heterochromia had and has long been emphasized. Later studies on dark eyed populations have raised questions on the importance of this clinical feature and have caused a shift in the nomenclature. More than 100 years have passed since Fuchs' article and several extensive reviews have been published in an attempt to answer remaining questions concerning Fuchs' uveitis[3, 6-8]. The clinical spectrum has been expanded by recognizing other features of the disease and remarkable progress has been

made in deciphering the puzzling etiology. A literature search reveals that recent information has not yet been summarized. This review will offer an overview of the recent findings and their implications.

1.2 MATERIALS AND METHODS

An online literature search was conducted using the PubMed database with the keywords "Fuchs' heterochromic", "Fuchs' uveitis", "ocular manifestations rubella". Search terms and their respective number of hits are listed in Table 1. References from relevant articles and books were also identified. Statistical analysis was done using the software available on statpages.org. The properties of anti-rubella antibody detection were calculated based on 2-way contingency table analysis (http://statpages.org/ctab2x2.html) (cf. Appendix 2). The principles of this analysis are based upon the textbook *Fundamentals of Biostatistics* by Bernard Rosner, 6th Ed., 2006.

TABLE 1: SEARCH TERMS (NUMBERS LAST CHECKED ON 02/23/2011)

Search term	Number of hits	Hits from last 5 years	Number of reviews
Fuchs heterochromic cyclitis	191	34	17
Fuchs heterochromic iridocyclitis	136	28	12
Fuchs heterochromic uveitis	175	29	13
Fuchs' heterochromic cyclitis	146	15	15
Fuchs' heterochromic iridocyclitis	106	12	12
Fuchs' heterochromic uveitis	141	14	12
Fuchs uveitis	303	54	26
Fuchs' uveitis	203	22	20
Fuchs uveitis syndrome	99	23	12
Fuchs' uveitis syndrome	61	6	9
Fuchs syndrome	662	159	56
Fuchs' syndrome	124	19	12
"fuchs heterochromic" AND "rubella"	10	7	-
"ocular manifestations" AND "rubella"	21	2	7

2. CLINICAL FEATURES

2.1 EPIDEMIOLOGY

Most patients with Fuchs' uveitis present in the third or fourth decade of life, without gender preference[9, 10]. It can however affect either eye in patients of all ages. An epidemiological survey in the Savoy (France) showed an annual incidence of FU of 0.9 per 100,000[11]. FU counts for 1.2 to 8.3% of all cases of uveitis[12]. No racial or geographical variations in incidence have been discovered so far, but epidemiological data on the general subject of uveitis tends to show large variations [2]. Especially the use of various classification systems hampers analysis of the retrieved epidemiological data. A standardized classification system would enable a more reliable analysis and could allow the detection of specific variations, for uveitis in general and more specifically for FU. In medical literature, several associations with between FU and other medical conditions have been suggested, but none of these have been sufficiently proved. Dernouchamps estimated that an ophthalmologist in Belgium would have to recognize one case of Fuchs' uveitis every 2 to 3 years[13].

2.2 TERMINOLOGY

Assigning a name to a disease such as Fuchs' uveitis does not merely concern a semantic subdivision, but it also influences diagnostics and treatment[14]. According to the IUSG guidelines (International Uveitis Study Group), it is best to base the uveitis classification on the main anatomical location of the inflammation, as several types of uveitis have no known etiology[15]. There is little consensus on the terminology of uveitis, which makes it even more difficult for a distinct entity of uveitis such as Fuchs' uveitis. It is often considered a chronic anterior uveitis. Indicators of an anterior uveitis – keratic precipitates, cells and flare in the anterior chamber – are indeed present in eyes with Fuchs' uveitis. These anterior segment manifestations (especially heterochromia) are the most obvious features, but FU is not a pure anterior uveitis[16]. In a retrospective study of 80 Fuchs' uveitis patients, Herbort noticed that posterior signs were even more frequent than anterior ones[16]. The eponym 'Fuchs' heterochromic (irido)cyclitis' (FHI/FHC) has long been used and emphasizes the most obvious features[3]. However, the condition can affect several parts of the eye, which is primarily shown by vitreous and even disc involvement[7, 17]. Therefore, FHC and FHI do not accurately describe this condition, which is why several authors prefer the broader term 'Fuchs' heterochromic uveitis' (FHU)[3]. Liesegang was the first to propose 'Fuchs' uveitis syndrome' (FUS)[18]. The term 'syndrome' may no longer be that appropriate. A syndrome is a characteristic cluster of signs and symptoms, whereas the pathophysiological mechanism of a disease is more or less known[14]. Given the recent findings on the etiology, the term 'Fuchs' heterochromic disease' (FHD) might be preferable. A recent article describes it as both a disease and a syndrome: the evidence for the role of rubella virus is convincing, but there is some remaining doubt whether this etiology may be generalized for all patients[14]. Franceschetti introduced the concise term 'Fuchs' syndrome', since heterochromia is not a constant feature[19]. Kimura suggested the name

'bilateral Fuchs' syndrome' since bilateral heterochromic cyclitis is a contradiction in terms[9]. It is remarkable to observe that authors have pointed out that since heterochromia is not always present, the adjective "heterochromic" should not be used. This was repetitively published as early as the 50s, but the adjective is still used. Other ocular disorders are named after Ernst Fuchs, which can make a simple term such as Fuchs' syndrome somewhat confusing[3]. Recently, the term 'Fuchs' uveitis' has been introduced, which differentiates it from Fuchs' endothelial dystrophia[16]. It also avoids overemphasizing heterochromia, which is striking when present but not disease-defining. For these reasons, the term FU will be used in this review from this point on.

2.3 Clinical symptoms at presentation

Patients are often unaware of the presence of FU, as it can remain asymptomatic for several years before diagnosis. It is usually insidious and subtle in its initial presentation. The principal symptoms are visual impairment and floaters, due to lens and vitreous opacities respectively[20]. Anterior chamber cells or vitreous debris may also be noticed during routine examination[10]. Few patients seek help because of an observed change in colour of the iris or because of spontaneous hyphema[2, 9, 21]. Patients generally do not complain of ocular pain or discomfort. When present, it is a poorly localized periocular or even hemifacial pain, but this is rather unusual[3, 21, 22]. Redness, photophobia and ciliary injection, which are typical symptoms in anterior uveitis, are very rare.

2.4 Clinical signs

Several authors have stated that diagnosis of FU is often difficult to make, since the various clinical signs are not always present at a given time[7, 13]. In fully developed cases with gross heterochromia, diagnosis is usually not problematic. More subtle presentations or somewhat atypical forms can however easily be missed. Little is known about the evolution of clinical features over time, for the reason that most studies have a limited follow-up period[3]. It has been reported that the signs can fluctuate and some can even disappear and reappear[3, 9, 11, 18]. The clinical spectrum of patients in different populations also seems to variate[20, 23-26]. Both racial and environmental factors may contribute to these observed differences[20]. Further investigation of these clinical variations could offer additional insights but this lies beyond the scope of this review. An overview of the clinical signs is presented here, divided into paragraphs according to the basic ocular anatomy. These elements are limited to the eye, as FU patients typically exhibit no signs of systemic disease.

2.4.1 CORNEA

Keratic precipitates on the corneal endothelium are commonly seen in FU eyes, scattered over the entire surface. These small, grey-white or translucent (non-pigmented), mainly stellate precipitates are sharply circumscribed with fibrillary extensions, never confluent and connected by interposed filaments[2, 7, 21, 22]. These precipitates usually do not affect vision, which explains the patients' unawareness of their presence[6]. Occasionally, they are sufficiently dense to disturb light transmission but this occurs very rarely[1]. They are not concentrated in the triangle of Arlt, as in several other types of uveitis[2, 10]. Authors often describe these precipitates as almost pathognomic of FU, but they are less stereotypical than often described. Other distributions (more central or more inferior) have been sporadically described and the size and distribution tends to vary in the course of time[21]. Sometimes, they even spontaneously disappear or reappear, days up to years ater lens extraction[7, 13, 18, 21]. It is yet unclear whether the morphologic heterogeneity reflects an intrinsic diversity or a different duration or treatment of the disease[27]. Correlation with CMV infection and with high levels of cellular and humoral immunity against corneal antigens have been suggested as explanations for the variations in keratic precipitates in FU[20, 26]. In vivo confocal microscopy(IVCM) has demonstrated that clinically round precipitates also have a stellate aspect[27]. In Dutch literature, keratic precipitates are sometimes referred to as 'Descemet spots'. The use of this term should be avoided , as the spots are situated on the corneal endothelium and not on the Descemet membrane[28]. Even though FU used to be considered a nongranulomatous condition, several authors nowadays believe that based upon the keratic precipitates (and the iris nodules cf. infra), FU is rather a granulomatous uveitis[20]. Mutton-fat precipitates, typical for granulomatous uveitis, occur rather rarely in FU eyes. Keratic precipitates can be described as granulomatous when they can be individually distinguished, which is the case in FU[29]. Other corneal abnormalities such as corneal edema and larger areas of endothelial abnormality have been described in FU patients in the past, but are no longer mentioned in more recent reports[9, 18, 19].

2.4.2 ANTERIOR CHAMBER

A mild anterior chamber reaction is often observed in FU eyes. This chronic activity is mainly cellular, flare is less frequently found[7, 9, 21, 22, 30, 31]. The encountered cells are mostly lymphocytes and plasma cells with a small amount of histiocytes, monocytes and neutrophiles[6, 13]. The activity can fluctuate over time: more acute episodes occur but the reaction may even be absent at times[2]. Loss of all signs of intraocular inflammation after cataract extraction has been observed in a subset of Jones' patients[30]. This, albeit isolated, observation remains unexplained: a causal link with cataract surgery has been suggested, but it may merely represent a transient, quiet period[3]. Studies performed by Amsler in 1946 showed that fluoresceine administered systemically appeared in the FU eye more rapidly[3]. This observed disruption of the blood-aqueous barrier was later confirmed by showing leakage of the iris vessels. Iris capillaries have a nonfenestrated endothelium and hence should not leak IV administered fluorescein, although patients above 50 can show some peripupillary leakage as an epiphenomenon of ageing . Leakage was mainly observed in

newly formed vessels but also in FU eyes without neovascularization[7]. The increased permeability was also examined by means of laser flare photometry: the measured values were minimal and remained quite stable during follow-up[20].

2.4.3 IRIS

2.4.3.1 THE NORMAL IRIS

An understanding of the iris anatomy is necessary to appreciate the changes that occur in FU. The iris consists of two layers of a different embryological origin. The anterior stroma is mesodermal and consists of connective tissue with fibroblasts, melanocytes and the sphincter and dilator muscles. In contrast, stromal melanocytes originate from the neural crest. The posterior surface of the iris is built up by neuro-ectodermal pigment epithelium: two layers of cuboidal, strongly pigmented cells that intrude into the pupil as the pigment ruff. The anterior border layer of the stroma is often discussed separately. This stromal condensation is discontinued in several crypts and strongly varies in pigmentation[30]. Three factors of the iris structure influence the eye colour: the pigment epithelium (especially significant in albinism), the stromal density and the pigmentation of the stroma. The density mainly affects colour in blue eyes: longer wavelenghts are absorbed by the pigment epithelium whereas the short, blue wavelenghts are scattered by the stroma. The texture of the iris surface is more prominent in blue eyes: the fibrillary structure of the stroma is apparent, as are the radial vessels and sometimes the sphincter and dilator pupillae[6, 30]. The pigment content of the most anterior part of the stroma is highly important in other eye colours[32]. In dark eyes, the melanocytes in this anterior layer are strongly pigmented, so that the structure of the underlying iris layers remains hidden[30]. These features usually show great similarities between both eyes. It is not exceptional to find naevi in one eye but not in the contralateral, but large differences in colour or structure are rare[6].

2.4.3.2 INFLAMMATION

The inflammatory component of this disorder is mild and chronic without acute, manifest signs of inflammation such as pain, miosis or photophobia[7, 9, 19]. The affected eye is white and quiet, without ciliary injection[21]. Microscopic studies have confirmed the presence of inflammatory cells in the iris stroma, the anterior border layer, the anterior chamber, the ciliary body and sometimes even the trabecular meshwork (cf. Immunology and pathogenesis). The character and course of this inflammation is a typical, constant feature of FU[4, 9]. Fuchs himself also considered cyclitis, inflammation of the ciliary body, to be the essential characteristic of the disease[2][5].

2.4.3.3 IRIS ATROPHY

The observation that heterochromia is not always clearly present, has drawn more attention to the specific yet subtle iris changes. This atrophy is one of the most constant signs of FU, present in nearly all FU cases[21]. It is typically diffuse, starting in the area adjacent to the pupil[11, 13]. A sectoral pattern strongly suggests a different diagnosis[30]. All layers of the iris – the anterior border layer, the stroma and the posterior pigment epithelium – lose pigment and volume[18, 21, 30]. Atrophy of the anterior border layer manifests in the early stages of the disease, at times resulting in a complete depigmentation of this layer[30]. Radial markings at the pupillary border can become less prominent[9]. The iris loses its sharp detail and looks somewhat pale[1]. The iris surface becomes smoother, due to the blunting of the surface rugae and absence of the crypts[7, 8, 18, 33, 34]. Deeper structures beneath this surface such as radial vessels and the sphincter pupillae can become more noticeable[2]. The pupillary pigment ruff sometimes appears defective, which gives it a moth-eaten appearance and makes the pupil somewhat irregular[18, 30]. Advanced, patchy atrophy of the posterior pigment epithelium, with a predilection for the iris periphery, can cause irregular transillumination defects[9, 13, 18, 21]. A similar process takes place in the ciliary body[7]. The atrophy is difficult to trace in bilateral cases, as there is no healthy eye to compare with[22]. Careful slit-lamp examination is often necessary to visualize differences in detail. When FU is suspected, patients should also be examined in natural light, prior to pupillary dilatation, as this can highlight more subtle differences in iris texture[10]. The sphincter and dilator muscle fibers may also be involved, which can result in anisocoria with an irregularly shaped pupil[2, 7, 10, 18, 30]. These pupillary irregularities mainly manifest in later stages of the disease, with areas of sclerosis and thinning of mainly of the sphincter muscle[2]. As mentioned above, the ciliary body is also affected in FU. The pathologic changes have long been neglected because of difficulties in visualizing this tissue. High frequency ultrasound biomicroscopy (UBM) has demonstrated exsudates in the ciliary body and in the basal vitreous body[25, 35]. Ciliary inflammation should not be forgotten as a feature of FU, just because routine examination cannot establish this ciliary involvement.

2.4.3.4 HETEROCHROMIA

The clinical feature that was long at the center of interest and accounts for many of the names, is heterochromia. Iris atrophy of especially the most anterior layer is responsible for this gradually developing sign[30]. In FU, heterochromia iridum occurs, a difference in eye colour between both eyes. This contrasts with heterochromia iridis, which represents colour differences within the same eye[7]. Usually, this heterochromia is acquired, but it has been reported to be present at birth[18, 30]. In the majority of Fuchs' 38 patients, it was said to be congenital[1]. The two forms (congenital and acquired) do not show any clinical differences[30]. Patients may be uncertain about the time of onset, anamnesis can therefore be unreliable[22, 30]. Some authors merely speak of hypochromia, which is somewhat simplistic. In most cases, the lighter eye is indeed the affected one. A brown iris will appear less brown, but in patients with blue eyes, inverse heterochromia can be present. The loss of pigment aggregates exposes the dark posterior pigment epithelium,

which causes deepening of the blue colour[1, 7, 10, 30]. In general, heterochromia is more difficult to recognize in dark-coloured eyes, because the anterior and posterior part of the iris then have a similar colour[1-3, 9, 19, 30]. The marked pigment content requires a more profound atrophy in order to result in a clinically visible colour difference. Atrophy in brown eyes may also make the pigment epithelium apparent, which can even lead to a darker aspect[33]. It should be emphasized that heterochromia is not always present and that it is not a requirement for diagnosis[9, 23]. In regions with predominantly brown eyes such as Saudi Arabia, China, and Mexico, heterochromia was only reported in 13.9%, 14% and 25.3% respectively[25, 33, 35]. The colour difference can be absent in both brown and blue eyes, but especially occurs in bilateral cases and brown irides[13, 18]. The presence of heterochromia does not appear to be associated with a worse prognosis[35]. Whether heterochromia is obvious or not depends upon the extent of atrophy, the original eye colour, the amount of pigment (primarily in the anterior border layer) and uni- or bilaterality[10].

2.4.3.5 BILATERAL CASES

FU is mostly unilateral, but the minority of bilateral cases (approximately 10% of the patients: cf. table 2) should not be forgotten. Comparison with the opposite eye can be used as a help in diagnosis, but this is no longer possible in bilateral cases[30]. Loewenfeld and Thompson also stated that statistics on this aspect cannot be easily compared: reported frequencies will be higher if bilaterality is specifically searched for, but it will be overlooked if unilaterality is considered an essential feature[6]. This emphasizes the importance of uniform diagnostic criteria. In Norrsell and Sjödells cohort, bilateral cases had a more serious condition. The authors were unable not explain this observation. Franceschetti also felt that bilateral cases developed complications more often[19]. Unilateral cases at presentation have not been reported to become bilateral, which can be reassuring[22, 23].

TABLE 2: PREVALENCE OF BILATERAL FU PATIENTS

Publication	Percentage bilateral cases
Fuchs (1906)	7.9% (of 38 patients)
Loewenfeld and Thompson (1973)	11.7% (of 921 patients)
Dernouchamps (1984)	8.1% (of 550 patients)
Tabbut et al (1988)	6.0% (of 67 patients)
Silva et al (1988)	21.21% (of 132 patients)
Jones (1991)	7.8% (of 103 patients)
Fearnley and Rosenthal (1995)	15.6% (of 77 patients)
Arellanes-Garcia et al (2002)	10.3% (of 68 patients)
Quentin and Reiber (2003)	6% (of 52 patients)
Yang et al (2006)	13.5% (of 104 patients)
Norrsell en Sjödell (2008)	6% (of 54 patients)
Tugal-Tutkun et al (2009)	5.2% (of 172 patients)
Bouchenaki and Herbort (2009)	11.4% (of 105 patients)
Kanavi et al (2010)	17.6% (of 34 patients)
Al-Mansour et al (2010)	4.8% (of 166 patients)
Bouchenaki and Herbort (2010)	12.4% (of 39 patients)

2.4.3.6 IRIS NODULES

The prevalence of iris nodules in FU ranges from 20% to 31.5%[35, 36]. This percentage seems to be higher in populations with predominantly brown irides than in patients with light-coloured eyes, potentially because nodules are more easily missed in blue irides[14]. As they are small and fairly translucent, they may sometimes be overlooked[3]. Two types of nodules can be found: Koeppe nodules are small, white spots at the iris margin, whereas Busacca nodules are evenly distributed within the stroma, especially in the sphincter area[7, 8, 20]. In FU, Koeppe nodules are more common than Busacca[20]. Their frequency does not seem to correlate with the severity of the inflammation[30]. Jones felt they were more often present in earlier stages (without iris atrophy or cataract), but later authors did not observe the same trend[3, 20]. Transient synechiae can occur together with Koeppe nodules, but these are evanescent and merely leave residual pigmented lines

on the anterior lens capsule[1-3, 30]. Such a trail of radial pigment lines can suggest a diagnosis of FU[3]. Histopathologically, the nodules appear to comprise aggregates of plasma cells[34]. These iris nodules can cause trouble for differential diagnosis. FU is classically classified as a nongranulomatous uveitis, whereas (especially Busacca) nodules are usually only found in granulomatous uveitis[8, 19]. This is particularly a problem in black patients, as heterochromia is often absent in this group[23]. Typical nodules in granulomatous uveitis are larger and present in smaller amounts, irregularly shaped (fluffy) and sometimes buried within the stroma[25, 37]. It is of importance that the nodules in FU do not lead to persisting synechiae and that unilateral uveitis is not typical for uveitis associated with systemic granulomatous disease such as sarcoidosis[23, 35, 36]. Small, refractile crystalline deposits (so-called Russell bodies) can sometimes be detected on the anterior iris surface, as in other types of chronic uveitis[3, 8]. These crystals consist of plasma cells, packed with immunoglobulin, which is a signature of the inflammatory activity.

2.4.4 ANTERIOR CHAMBER ANGLE

Few new elements were added to the clinical entity in the years following Fuchs's original article, which shows how elaborate and accurate his work was. In 1946, Amsler and his colleagues were able to find a new feature of FU[30]. They observed a small, filiform hemorrhage originating from the chamber angle or the irisroot during paracentesis in 22 of their 23 FU patients. This hyphema typically occurred near the chamber angle, opposite to the point of entrance[7, 13]. It was long considered pathognomic for FU and is referred to as the Amsler sign. This bleeding has been reported following mild trauma, peribulbar anesthesia, contact tonometry, surgery, mydriasis, gonioscopy and even spontaneously[8, 10]. Later studies however showed that it is not pathognomic, since it also occurs in other ocular conditions, such as ocular sarcoidosis[2, 8, 13]. The absence of this feature does not exclude FU, but the occurrence does make the diagnosis more likely[2, 3]. A diagnostic paracentesis in order to evoke this bleeding, which has been done by ophthalmologists in the past, should not be performed for this purpose[3, 7]. The reason for the distinct tendency to bleed has yet to be revealed. Amsler stated that the sudden reduction of anterior chamber pressure during paracentesis would cause bleeding from fragile vessels. Such small, delicate vessels have indeed been found bridging the anterior chamber in FU[13, 18]. Curiously so, the occurrence of this bleeding is not strictly correlated with iris neovascularization or with abnormal angle vessels[18]. Henkind found fine vessels – circular and radial – in the chamber angle of more than one third of 269 normal eyes[7, 38]. This shows that it is uncertain whether such vessels are truly pathologic.

Neovascularization is recognized as a feature of FU, both in the iridocorneal angle and in the iris[1, 18]. Its incidence is uncertain: normal variations in iris vasculature are difficult to interpret, atrophy can make normal vessels more prominent and preexisting vessels may be altered in the course of FU. It has been a subject for debate whether the vessels in FU are neovascular or merely abnormal. The vessels seem to have a different appearance than in rubeosis iridis. Rubeotic vessels appear in a branched pattern, whereas the vasculature in FU has a patchy and discontinuous aspect on iris angiograms[2, 21]. Anterior segment

fluorescein angiography (FA) has demonstrated perfusion defects and peripupillary leakage of dye from iris vessels, without vascular abnormalities in the opposite, healthy iris[1, 3]. Areas of delayed perfusion are considered as regions of focal ischemia, potentially leading to neovascularization in advanced cases. Leakage from iris vessels could account for some of the flare observed in FU. Angiographic studies in patients with chronic anterior uveitis have shown that neovascularization in the chamber angle, next to leakage of iris vessels, is not specific for FU[39]. This implies that increased vasculature is neither sensitive nor specific: it is not a constant feature and it also occurs in other types of uveitis. The ciliary body is also affected by similar changes. Abnormal vessels and blood-filled cysts have been demonstrated in the ciliary body[1]. There is remarkably less information available in literature on these alterations compared to the iris changes. Small peripheral anterior synechiae (PAS) are sometimes found in the chamber angle of FU patients (occasionally in non-operated patients), but these are, for reasons somewhat unknown, not correlated with neovascularization[2, 18]. The presence of PAS on gonioscopy does not seem to relate to the incidence and severity of secondary glaucoma, even though theoretically, anterior synechiae can impede aqueous outflow and thus result in glaucoma[18].

2.4.5 LENS

Cataract frequently develops in FU, typically in the posterior subcapsular region[7]. Both anterior and posterior chamber inflammation are known to promote lens opacification. This topic is further explored in the paragraph on complications. The strict absence of posterior synechiae, despite chronic inflammatory activity, is very typical for FU[9]. Such synechiae can however appear after intraocular surgery[9, 30]. They occasionally have been reported in FU patients with secondary glaucoma[9].

2.4.6 VITREOUS CAVITY

Vitreous involvement in FU has long been underrated, even though it can cause visual problems. Cells and strands are frequently found in the vitreous, especially in the anterior regions. These are usually white and not brown as in other types of uveitis and can be diffusely present[19]. Many patients have obvious dustlike opacities with possible veil formation, but only few cells[22]. The density of the inflammatory debris can vary over time and may progress to the formation of so-called snowballs[3]. This is opposite to the activity in the anterior chamber, where cells are more present than flare. The vitreous inflammation is even more marked than anterior chamber activity[29]. It was already described as a clinical sign by Fuchs, but was rather neglected in subsequent studies because the focus was directed towards the anterior segment[10]. Bouchenaki and Herbort revived the interest in vitreous involvement in FU and even observed vitreous infiltration in 97.4% of their FU patients[16]. Manifest cataract formation can sometimes inhibit proper examination[19, 20, 30]. A lack of attention for this vitreous involvement may have diagnostic consequences: if the anterior signs are less marked than the vitreous activity, this can lead to an erroneous diagnosis of intermediate uveitis[8]. The initial presentation with floaters and blurred vision can resemble that of intermediate uveitis, next to the

predominant unilaterality and the similar age group[1][3][4]. The absence of macular edema in FU is very important in differentiating these types of uveitis.

2.4.7 FUNDUS

The consistent absence of cystoid macular edema in FU is striking. Despite chronic inflammation, it is only described in FU patients following intraocular surgery. The occurrence of chorioretinal scars has been reported in FU patients, in the affected but also in the healthy contralateral eye or in both. The reported prevalence of the lesions is very variable (from 7.2% to 65%)[1]. These lesions are similar to those observed in ocular toxoplasmosis: focal lesions of retinal pigment epithelium atrophy with hyperpigmented borders[23]. They are usually small, half of the disc diameter and are mostly situated in the peripheral retina[30]. This finding has led to suggestions involving a causal relationship between Toxoplasma gondii and FU (cf. infra)[21, 40]. The fundus structures generally have a normal function and structure in FU. Venous sheathing was described by Liesegang, who encountered it in 6 of his 54 FU patients[18]. He stressed that this mild, midperipheral sheathing could be overlooked owing to the presence of cataract and that 2 of these patients had (probable) MS[18]. This seems to be an isolated finding, which raises doubt on the existence of a real correlation. Retinal break and detachment have been found in increased incidence in FU patients compared to a general population[16, 41]. More studies are required to confirm this finding and to quantify the additional risk. Fundus fluoresceine angiography has been recently introduced in order to examine FU patients. Yang et al found disc staining and leakage of the midperipheral retinal capillaries in 68% and 60% of 25 eyes respectively[25]. Bouchenaki and Herbort discovered retinal vascular leakage in 13.6% and disc hyperfluorescence in 97.7% of the cases[16]. In most cases (60.5%), this was mild and did not seem to correlate with disease duration or the extent of vitreous involvement. Tugal-Tutkun et al only detected hyperfluorescence of the optic disc in 7 of 32 eyes (22%)[20]. Few hypotheses have been formulated to explain this feature. An inflammatory breakdown of the blood-eye barrier may be responsible or a severely affected vitreous could cause traction. This second option seems less likely, taking into account how obvious disc hyperfluorescence appears to be even in cases with limited vitreous involvement. Tugal-Tutkun et al have confirmed subtotal posterior vitreous detachment in a few FU eyes exhibiting hyperfluorescence[20]. The presence of disc hyperfluorescence could confuse clinicians, as it is not a well-known association. An electroretinographic study on FU eyes has previously demonstrated subclinical damage to the inner retinal layers, despite a good VA[17]. These findings stress that FU is not limited to the anterior segment.

2.5 DIAGNOSTIC CRITERIA

There are no internationally accepted diagnostic criteria for FU. Although an adequate laboratory test is alluring, diagnosis of FU is still made on clinical grounds, based on a thorough opthalmological examination[2, 14, 35]. The subjective appraisal of coexisting clinical features should allow the diagnosis FU to be made. The classical features in a fully developed case are threefold: heterochromia, cyclitis and cataract[9,

[29]. This triad however does not adequately describe the variable clinical spectrum of FU: it is incomplete and incorrect at times. It usually takes several years for the three features to manifest, which makes early diagnosis impossible when applying these three criteria. Broadening the diagnostic spectrum is necessary to prevent medical practitioners from overlooking FU[3]. Diagnostic delay is often referred to as an important problem. This is however somewhat incorrect, as FU is a benign condition that does not require treatment. Misdiagnosis is more common, and may lead to potentially harmful treatment[14]. Studies have mentioned a correct initial diagnosis in 63.1% and 50.6%, with a mean delay of diagnosis of FU of 3.4 and 6.7 years respectively[22, 30]. It is interesting to contemplate why this occurs. The overappreciation of heterochromia has already been addressed: it is obvious in some cases, but in other ones it is very subtle or even absent[9, 30]. Additionally, assessment of heterochromia is observer-dependent and the time of appearance will highly depend upon the initial eye colour[22, 30]. In a recent editorial, heterochromia in FU is wonderfully described as "the tree which prevents the forest being seen"[29]. It should therefore play little role within diagnosis. Subtle changes of the iris surface are more helpful in diagnosing FU, as they are a more sensitive and reliable sign[18, 20-22]. Macroscopic heterochromia can serve as a confirmation of this finding[30]. Cataract develops in later stages of the disease, which limits its use in diagnostics[9]. The perception that the vitreous is of little significance in FU is reflected in several ophthalmology textbooks[3, 22]. Significant vitreous opacification draws the attention to the posterior uvea, so that FU is not considered as a diagnosis[22]. This is obvious when comparing conditions mentioned in textbooks for differential diagnosis. These are usually only types of anterior uveitis, but not intermediate uveitis[29]. However, vitreous opacities frequently cause initial symptoms and can be substantial, even requiring vitrectomy. Whereas iris atrophy is perceived as necessary for diagnosis of FU, vitreous opacities are not strictly obligatory. Recent studies focus on the absence of heterochromia and the presence of vitreous opacities as the main causes for misdiagnosis. Bouchenaki and Herbort found that in more than 70% of the misdiagnosed FU patients, uveitis of the posterior segment was the initial diagnosis[16]. Another triad was suggested, offering a certainty of almost 100%: heterochromia, keratic precipitates and vitreous opacities. When iris atrophy and vitreous opacities are present and cystoid macular edema and posterior synechiae are absent, then the diagnosis of FU is quite certain. CME and posterior synechiae are useful exclusion criteria: their presence in patients without a history of intraocular surgery excludes FU.

There is certainly reason for revising the diagnostic features and defining clear, internationally accepted criteria for FU in order to reduce misdiagnosis. Failure to recognize FU has important implications. FU substantially differs from other types of uveitis in terms of diagnostic work-up, management and prognosis[7, 21, 30]. Extensive and fruitless work-up, which is both expensive and time-consuming, can be avoided by promptly acknowledging a uveitis case as FU[9, 22]. The patient can be reassured because FU has a fairly benign course[9]. An international workshop on Fuchs' uveitis, as suggested in a recent editorial, could create a more uniform approach[29]. Possible racial variations should also be investigated in this regard. The lack of

uniformity also hampers comparison of data. If different clinical criteria are used for patient selection, it may be incorrect to compare data from various studies[7].

3. COMPLICATIONS

3.1 CATARACT

Cataract is the primary cause of visual loss in FU. The discovery of this secondary cataract is often the reason for diagnosing FU itself. It usually starts in the posterior subcapsular area and seems to be virtually inevitable in longstanding FU as it correlates with the chronicity of the inflammation[18]. Incidence rates range from 15% to 80.2%[30, 42]. This broad variation can be explained by differences in follow-up period and in the duration of diagnostic delay[11, 30]. The type of cataract seems to be similar to that secondary to other types of chronic uveitis or to corticosteroid treatment[1, 43]. The causes are no different (inflammatory activity and use of steroids), except for the lack of synechiae typically seen in (non-operated) FU eyes.

3.1.1 SURGICAL PROCEDURE

Considering the fairly young age of these patients, surgery is indicated at an earlier stage than in age-related cataract. The surgery in itself is technically no more difficult than a routine cataract procedure as FU eyes respond well to surgical trauma[9, 43, 44]. Several reports on cataract extraction in FU patients have been published and show better surgical outcomes than in cataract secondary to other types of uveitis[1][2, 45]2,51. Early reports showed conflicting results. Initially, authors concluded that surgery was highly uneventful, merely associated with transient hyphema[9, 19]. However, these reports did not offer sufficient information on the length of follow-up period, the type of surgery performed or the management of inflammation perioperatively[43]. Other authors reported on extensive complications following intra- and extracapsular cataract extraction(ICCE and ECCE): vitreous loss or hemorrhage, corneal edema, hyphema, postoperative uveitis and progressive glaucoma[43]. Intraocular lens implantation (IOL) was later introduced, despite the concerns of implanting an IOL in an inflamed eye. FU seems to be an exception: FU is one of the rare types of uveitis amenable to IOLs, as the eyes behave less agressively. A few studies on the insertion of iris-supported IOL were published. Results were acceptable, with no severe complications in the limited follow-up period[43]. However, the use of these iris-fixated IOLs has become limited in view of the iris abnormalities in FU[1]. Insertion of anterior chamber IOLs in FU eyes has not been well documented, but it is to be expected that such lenses should be used with caution[2]. Publications on the comparison of ECCE with and without posterior chamber IOL(PC IOL) showed few complications and a good visual prognosis[19]. Some authors considered the use of PC IOL to be an additional risk, based on a higher level of complications. Jones and O'Neill et al especially related an increased risk for severe iris atrophy, secondary glaucoma or severe iris vessel abnormalities[46, 47]. Other reports failed to show significant complications related to the

IOLs and found better visual outcomes in pseudophakic compared to aphakic patients[3, 48, 49]. Postoperative anterior uveitis due to IOL insertion did not appear to affect the visual outcome[49]. More recent reports on PE with PC IOL continue to show encouraging results. Sporadically, visual outcome is worse than expected. Velilla et al only achieved a visual acuity of 6/12 or better in 45.4% of their patients (11 in total)[24]. Reports on larger patient cohorts as in the study of Tejwani et al (103 FU patients) generally show good visual outcome: after 5 weeks, 88.3% of their patients reached a visual acuity of 6/12 or better[49]. Another option is secondary IOL implantation, usually due to contact lens intolerance. Preoperative requirements are inflammatory control and an intact posterior capsule. As the results were satisfactory, it seems to be a safe procedure but this is merely based on 1 report on 4 patients[50]. When comparing reports on cataract extraction in FU patients, a couple of potential confounders should be kept in mind. Since the number of FU patients undergoing cataract extraction annually is limited, most studies report on series of patients over several years. This makes the comparison of study results difficult, as surgical techniques have developed rapidly in the last decades. The criteria for diagnosing FU may also be inconsistent over time. The follow-up period is often quite limited, therefore late complications might be missed because of this. Additional specific reports, containing information on more than merely the visual outcome or the rate of complications, have increased the knowledge of the impact of cataract extraction in an FU eye. Flare measurements using laser flare photometry revealed a postoperative increase of flare but this decreased in a later stage and remained stable until the end of the follow-up period (6 months after phacoemulsification with PC IOL)[51]. This confirms the clinical observation of a lack of difference in inflammatory activity between the pre- and postoperative state, as reported by Soheilian et al[42]. Phacoemulsification seems to cause a mild and rapidly reversible breakdown of the blood-aqueous barrier. Studies on the comparison of different types of IOLs have been performed on uveitis patients, but not specifically on FU patients. The uveal and capsular biocompatibility of hydrophobic acrylic, hydrophilic acrylic and silicone IOLs has been evaluated but no type of IOL has led to the best results on both parameters[8]. Due to this lack of specific data, it is not yet possible to point out which type of IOL is the most adequate in FU eyes. In 33% to 100% of FU eyes, deposition of pigment or debris on the IOL has been reported, but this only leads to visual loss in severe cases[1, 2, 45].

3.1.2 POSTOPERATIVE COMPLICATIONS

The main complications in FU patients following cataract extraction are hyphema, posterior capsule opacification, vitreous hemorrhage, glaucoma and vitreous opacification[43]. Posterior synechiae can develop postoperatively, which indicates that FU no longer protects the inflamed eye from these synechiae after surgery[30, 42]. Its occurrence does not seem to correlate with the type of surgical procedure or with any type of complication[44]. Cystoid macular edema, a possible complication in uveitis patients in general, has an incidence in FU patients that is lower than in other types of uveitis but higher than in age-related cataract[44]. Postoperative uveitis develops in 20-35% of the cases following ECCE with PC IOL[44, 45, 52]. The

inflammatory activity is usually mild but may be associated with a pupillary membrane[2]. Jones even observed the disappearance of all inflammatory signs in 16 FU patients following cataract surgery, a phenomenon also observed by Franceschetti but without obvious explanation for it[19, 30].

The main cause for postoperative decreased vision is vitreous haze[8, 24, 34, 45]. The link between cataract extraction and the high occurrence of vitreous opacification has been a subject of discussion. Some authors claim that it is merely the result of extracting the cataractous lens that prevented the detection of pre-existing opacities[43, 44]. It may, on the other hand, be a reflection of the influence of surgery. Some authors indicated that vitreous flare can become condensed, possibly because of intraoperative bleeding from the ciliary body[18]. This is very difficult to assess, as it is a part of the natural course of FU. The high prevalence of vitreous opacities in FU patients offers a rationale for combining cataract extraction with a vitrectomy. Two reports have described the combination of these procedures in a selected subset of the patients[24, 44] . Assessment of the vitreous and performance of vitrectomy if indicated, proved to be favourable for visual rehabilitation. A necessity for vitrectomy some period after cataract extraction has been described in FU patients who were not satisfied with the visual results[22]. Combination surgery seems useful in shortening the duration of rehabilitation and reducing the number of procedures. Hyphema is reported in 3.6% to 76% of operated FU eyes. The significant differences in prevalence is partly due to the retrospective nature of most reports: a subtle, insignificant hemorrhage may remain unnoticed or unnoted by the surgeon[44]. This hemorrhage, probably the result of a sudden IOP reduction, is usually not significant enough to disturb surgery. Some do consider a substantial hemorrhage to be a warning of postoperative problems, most notably postoperative uveitis and glaucoma[3]. Preoperative detection of abnormal vessels on the iris or the chamber angle does not appear to reliably predict the occurrence of this hyphema[44]. It is therefore unnecessary to search for such vessels preoperatively, as they do not appear to have any predictive value.

The most important complication of cataract extraction is glaucoma, considering the frequency and the uncertain prognosis. There has been much debate on the relationship between cataract extraction and glaucoma. Some authors believe that this postoperative glaucoma reflects the natural course of the disease as the prevalence of elevated IOP postoperatively (about 3-35%) and the incidence of glaucoma in the FU population (about 15-50%) do not substantially differ[2, 43, 48, 53]. Others feel that surgery does have an impact on the aqueous humour dynamics and that the IOP elevation is related to the procedure[18, 43, 54]. The reported percentages of postoperative glaucoma seem to be comparable to those in other types of uveitis, but this finding does not shed any light on the relative impact of CE and uveitis itself in causing secondary glaucoma[53]. The prevalence of raised IOP following cataract extraction is mostly based on reports with variable and often limited follow-up periods. It is often not specified whether the term glaucoma is used in case of IOP elevation or only if there is associated optic disc cupping and/or visual field loss. Comparing data may be hazardous for these reasons. The exact impact of surgery on the IOP has therefore yet to be

clearly determined[43]. A large-scale, prospective study with a more extensive follow-up period could provide more reliable information. Glaucoma can develop postoperatively, but it may already be present prior to surgery. In these cases, gonioscopy is required and attempts should be made to medically lower the IOP prior to surgery[43]. Response to glaucoma treatment does not seem to be influenced by CE[53]. Combined filtration surgery and cataract extraction have been successfully performed, this offers the possibility of reducing the number of interventions[53]. However, some authors felt that this combination could lead to an increased risk of surgical failure and advised to perform the cataract extraction first[10].

In conclusion, cataract extraction in FU is of little concern and is associated with a good visual prognosis and few complications. Phacoemulsification with IOL implant is a safe procedure, the advantages of a PC IOL seem to outweigh the risks. The intraocular pressure is the main concern, and should be closely monitored[10].

3.2 GLAUCOMA

Secondary glaucoma is the most troublesome complication in FU and can lead to permanent visual loss. Reported prevalences show large variations, partly due to differences in the applied criteria of glaucoma and in follow-up period[22, 53]. Loewenfeld and Thompson, Dernouchamps and Liesegang observed glaucoma in 15.1%, 18.6% and 59% (incidence) respectively, but it was not specified how its diagnosis had been made[6, 13, 18]. It is often unclear whether or not a difference is being made between glaucoma and an isolated IOP elevation without optic nerve damage and/or visual field defects[52]. This overlap makes it difficult to estimate the true incidence of glaucoma (with VFD and/or optic cupping) in FU patients. La Hey et al made a difference between a "glaucoma suspect" eye (with elevated IOP but no glaucomatous damage) and true glaucoma, but this distinction is rarely made[53]. Arrelanes-Garcia et al noticed elevated IOP at some stage of FU in 30.66% of their patients, but a diagnosis of glaucoma was only made in 4%[33]. In the cohort of Norrsell and Sjödell, these percentages were 24% and 11% respectively[22]. A publication on secondary glaucoma in uveitis patients revealed that FU accounted for 19% of the patients, which is substantially higher than the general proportion of FU patients[8]. Jones and Liesegang calculated the risk of glaucoma development in their respective studies: 0.5% and 4% per year following presentation[18, 54]. Glaucoma seems to be more prevalent in black and older patients and in bilateral cases[2, 6, 11, 13, 23]. However, these findings rest on observation and have not been strongly documented.

3.2.1 ETIOLOGY OF SECONDARY GLAUCOMA

There is no consensus on the aetiology of this type of secondary glaucoma. It is described as similar in its course and symptoms to the primary open-angle type and gonioscopy has shown that the angle is usually open[52]. The IOP elevation is often intermittent and subacute in the early stages before becoming chronic and may respond to topical corticosteroids[18]. Several possible causes have been reported: recurrent hyphema, neovascularization of the chamber angle, peripheral anterior synechiae, trabeculitis, trabecular sclerosis, collapse of the canal of Schlemm, corticosteroid treatment and cataract extraction but usually, no apparent

cause can be found[2, 3, 13, 23, 24, 52]. The individual importance of the several interacting factors is difficult to assess. neovascularization in the chamber angle is often observed in FU patients with secondary glaucoma[11]. This has led some authors to postulate that FU patients with neovascularization may be at higher risk of developing glaucoma[11]. However, this is merely a statement based on observation: the presence of fine vessels does not automatically implicate that these vessels are the cause of the IOP elevation[53]. Peripheral anterior synechiae are rarely present, and it is doubtful that when present, these synechiae greatly contribute to the development of glaucoma in FU patients. Histologic evidence of trabeculitis and trabecular fibrosis leading to increased outflow resistance has been documented in a few FU patients[1, 9]. Steroid-related elevated IOP has been described in FU patients, but information on the features (timing and quantity) of steroid treatment should be taken into account in order to correctly assess the impact of corticosteroids[21, 52]. Next to cataract extraction, the cataract itself has been reported to cause acute angle closure glaucoma. Phacolytic glaucoma has also been reported to occur in hypermature cataract[52]. In conclusion, several factors can cause glaucoma, and the main cause can vary with the stage of the disease[54].

3.2.2 MANAGEMENT

Few reports have been published specifically on the management of glaucoma in FU patients. It is usually only briefly adressed and little information is offered on surgical procedure, follow-up period or visual field/acuity. Most reports describe only small numbers of patients. Early authors such as Kimura et al and Liesegang felt that this type of glaucoma became refractory to medical treatment in the course of the disease[9, 18]. Recent publications seem to indicate a decreased need for surgery, but it still remains the most difficult aspect in managing FU patients[20, 22]. Initially, the IOP elevation can be controlled by medication, but filtering surgery often becomes necessary[43]. Medical treatment was not sufficient in 66%, 73%, 47% and 48% in the studies of Liesegang, La Hey et al, Fearnley and Rosenthal and Al-Mansour et al respectively[18, 21, 35, 53]. The exact type of medical treatment was usually not specified. When compared to primary open angle glaucoma (POAG), secondary glaucoma more often requires drainage surgery. Argon laser trabeculoplasty is only sporadically described because it is usually not successful and sometimes even contraindicated. The reported success rates of trabeculectomy in patients with POAG ranges from 75% to 90%, which is higher than in FU patients[53]. Liesegang and La Hey et al reported on sufficient IOP control following one filtration surgery in 57% and 72% respectively (21 and 18 patients in total)[18, 53]. La Hey et al also found that further damage occurred after successful surgery: in 9 out of 16 patients, additional visual field loss and/or increase in cup/disk ratio was observed despite IOP control. The authors supported early surgical intervention, as medical treatment often fails[53]. The main complication of filtration surgery in FU is bleb failure, as in uveitis patients in general[2, 23]. Both Jones and La Hey et al recommend the use of fibrosis-inhibiting drugs (such as 5-fluorouracil or mitomycin-C) in FU patients to inhibit this process, even though its benefit has yet to be proven in FU[53, 54]. The majority of operated patients have encouraging results but the main problem seems to be a subgroup of patients who respond very poorly to therapy. In the study of

La Hey et al, 6 out of 23 filtration surgeries were categorized as complete failures. 3 patients required 1 reoperation and 1 patient underwent 2 additional procedures[53]. Other reports confirm the need for repeated interventions in a minority of patients[3, 23]. Some patients even require enucleation in end-stage glaucoma[54]. It would be interesting to compare a group of succesfully operated patients with a failure group. Preoperatively assessable features could inform the surgeon and patient on the risk of postoperative problems. This requires studies with larger patient cohorts, specifically focusing on managing glaucoma in FU.

3.3 VITREOUS OPACITIES AND VITRECTOMY

Vitreous opacities are a frequent feature of FU and can cause decreased vision and floaters. These can be especially disturbing following cataract extraction. Pars plana vitrectomy (PPV) may become necessary in order to eliminate these symptoms[8]. Waters et al studied 13 FU patients who underwent pars plana vitrectomy due to symptomatic opacities[55]. No severe complications (retinal detachment, choroidal ischemia or cystoid macular edema) were encountered. Scott et al reported similar results for their 12 FU patients[56]. PPV mainly has a symptomatic effect rather than influencing the inflammatory activity itself. A vitrectomy can safely be combined with cataract extraction when required[55, 56]. As in CE, results of vitrectomy in FU patients appear to follow a more benign course than in other types of chronic uveitis[8].

4. TREATMENT AND PROGNOSIS

The principle of 'primum non nocere' should always be kept in mind while managing FU, as it is often overtreated. Observation will do in the vast majority of FU patients. The mild inflammation does not seem to harm the intraocular structures[3]. Common longterm complications of chronic uveitis such as posterior synechiae and cystoid macular edema remain absent. Corticosteroids (CS) or other immunosuppressive agents do not cure FU nor do they improve the visual outcome[1, 10]. Randomized controlled trials(RCT) have not been performed on the effects of CS in FU but authors generally indicate a limited CS response in FU eyes[3]. CS therapy cessation does not appear to cause rebound of flare, which shows that it is safe to stop it[16]. The longterm use of non-steroidal anti-inflammatory agents has also been described, but no obvious beneficial effect could be determined and cessation of therapy did not lead to deterioration of symptoms[22, 24]. Treatment should be reserved to the complications of FU, not the inflammation itself.

In a few situations, a brief topical CS treatment can be indicated in FU. CS can be used in an attempt to control IOP, when it is believed that the degree of inflammation contributes to the pressure rise[21]. If patients exhibit a symptomatic increase in anterior chamber reaction, albeit exceptional in FU, a short CS treatment can diminish symptoms in these patients[10, 18, 21]. A short trial can be helpful in distinguishing FU from other

entities such as the Posner-Schlossman syndrome (PSS). The initial presentation may be somewhat similar but the CS response clearly differs[8]. Subtle heterochromia can occur in PSS, especially after repeated attacks but a small dose of CS causes a distinct IOP decrease in PSS[52]. The risks of CS treatment have to be kept in mind. In FU, cataract has the greatest impact on visual acuity and CS therapy can hasten the formation of cataract[23]. This impact is difficult to assess, considering the high incidence of cataract in FU. Glaucoma can also be induced in steroid responders[3].Cycloplegia can be used in order to facilitate vision in the early stages of posterior subcapsular cataract if cataract extraction is not yet indicated[7].

Prognosis is fairly good, even though FU is incurable[9, 35]. It has a chronic, mild course in which the inflammation itself does not cause symptoms but complications do. Most patients manage to retain a visual acuity of 6/12 or better in the FU eye. Cataract and vitreous opacities, the main causes of decreased vision, can be surgically cured. Al-Mansour et al reported on 166 FU patients and found independent predictors for better final visual acuity using univariate analysis: a shorter interval between the onset of symptoms and the presentation, a better initial visual acuity but more important, the absence of glaucoma at presentation and a lack of glaucoma surgery[35]. Glaucoma surgery was an independent significant predictor for a worse final visual acuity in multivariate analysis. These findings confirm that glaucoma is the true visual threat[9]. Regular monitoring is necessary for early detection of glaucoma. Patients should be motivated to adhere to regular follow-up, even if the patient is not under treatment or has no symptoms[21, 23]. Frequent screening of the IOP and the lens can assist in early detection of complications (glaucoma and cataract).

5. IMMUNOLOGY AND PATHOGENESIS

5.1 ULTRASTRUCTURE OF THE IRIS

Fuchs studied the histopathologic changes of 6 iris specimens and thus confirmed the clinically observed iris depigmentation. He also described a consistent, diffuse mononuclear infiltration of primarily plasma cells and lymphocytes, hyalinization and thickening of the blood vessel walls with narrowing of the lumen and occasionally Russell bodies[5]. Goldberg et al were the first of several authors to confirm these findings[57]. EM studies on iris specimens have showed a loss of anterior border cells, a reduction in the number of stromal melanocytes with smaller, irregular melanosomes and degeneration of the iris pigment epithelium[58, 59]. However, assessment of pigment cell loss on iris specimens is unreliable if the opposite, healthy iris is not examined simultaneously[60]. A degeneration of adrenergic nerve fibers and iris regions of necrosis have also been demonstrated[3]. Saari et al have confirmed this aspect by means of fluorescein angiography: newly formed vessels were found near infarcted regions of the iris[61]. These reports were unable to offer histopathologic criteria to differentiate FU from other types of chronic uveitis[62]. These studies have confirmed the inflammatory nature but were unable to detect micro-organisms. Findings can depend on the

chronicity of the disease: patients with longstanding FU may show more abnormalities[62]. Iris specimens are usually obtained during surgery, which is why mainly irides with advanced disease have been examined[63]. Observed changes in the ciliary body are stromal fibrosis and muscular atrophy, next to infiltration of plasma cells[1, 9]. A study on iris translucency showed a significantly elevated degree of intraocular straylight in FU eyes compared to the healthy eye[60]. This direct, non-invasive comparison allows for an objective confirmation of the relative difference. The technique has its limitations: other sources of elevated intra-ocular straylight (such as cataract and vitreous opacities), which are very frequent in FU, can cause faulty results.

5.2 CELLULAR COMPONENTS OF THE AQUEOUS

Quantative analysis of lymphocytes in the peripheral blood is of little importance in FU: investigation of the intraocular fluids and tissue is necessary to increase knowledge on the nature of inflammation[62]. Murray found a decreased activity of the T suppressor cells in the serum of FU patients (not a decreased number)[64]. Early reports have described the presence of mainly lymphocytes and plasma cells in the aqueous, next to smaller amounts of other types of immune cells (using centrifugation or millipore filtration)[13]. T lymphocytes account for most of the infiltrating cells with a high proportion of CD8+ cells[65]. Analysis of the TCR repertoire has showed that the CD8+ T cell expansion in the aqueous is characterized by a limited number of clonotypes[66]. These conclusions were based on the samples of only 2 patients, but do indicate an antigen-driven response. An increased level of interleukin-2 receptor (IL-2R), which is a marker of T lymphocyte activity, has been demonstrated in a high percentage of FU patients[67].

5.3 HUMORAL COMPONENTS OF THE AQUEOUS

Early studies revealed a relative increase of the gammaglobulin fraction (using electrophoresis) in the aqueous of 53.8% of 13 FU patients[1]. Studies have later demonstrated elevated IgG in the aqueous of FU patients, mostly IgG1[64]. Oligoclonal IgG1 bands reflect the characteristic local hyperproduction of IgG1, a subclass involved in T cell dependent responses. Dernouchamps and O'Connor have found immune complexes in the aqueous in respectively 22 of 28 patients and about 35% of the patients but not in the sera of these FU patients[1, 13]. This confirms the strict ocular location of the inflammatory activity. The cytokine profile of FU reflects the moderate immune activity and may explain the benign postoperative reaction of FU eyes. Differences in the cytokine profile of FU and IAU patients (idiopathic anterior uveitis) have been found : an increase in IFN-gamma and IL-10 and decreased IL-12 values were detected in FU patients[65]. Interestingly, IL-10 (a regulatory, anti-inflammatory cytokine) inhibites IFN-gamma (which mediates delayed hypersensitivity) production[65, 68]. IL-6 stimulates B lymphocytes for the local production of Ig: it was found in increased levels in the aqueous of FU patients but the mean IL-6 value was much larger in the toxoplasma uveitis group[69]. IL-12 is known to stimulate plasma cells for cytokine production. Its decreased

concentration may reflect a reduced cell-mediated immunity[65]. Several immunologic parameters (such as IgG, CRP, RF) have been tested in the peripheral blood of FU patients, but none of these showed abnormalities[67].

5.4 CHARACTERISTICS OF INFLAMMATION

FU responds differently to corticosteroids (CS) than most types of uveitis and is less aggressive. Authors have attempted to explain this through interpretation of differences in immune cells and cytokines. CS have a suppressive effect on several cell types, including macrophages. Both macrophages and CD4+ T cells have been found in significantly lower levels in the aqueous of FU patients than in patients with idiopathic anterior uveitis (IAU)[65]. Since T helper cells and macrophages are important target cells for CS, these results could partly explain the lack of steroid response. Leakage from iris vessels can also contribute to the amount of cells and flare and CS have no effect on this.

5.5 AUTO-IMMUNITY

Antibodies against ocular antigens have been reported in FU eyes. Remky detected anti-uvea auto-antibodies in the aqueous of FU patients, at 70x higher titers compared to the serum[70]. La Hey et al found antibodies against the corneal epithelium in 88% of 26 FU patients, compared to 1 out of 30 control patients[71]. Auto-antibodies against iris components have not been detected in sera of FU patients (by means of immunofluorescence). Detecting antibodies in the ciliary body is highly difficult due to the presence of endogenous immunoglobulin near the basal membrane. Van der Gaag et al (1989) studied the cellular and immunity against a 54 kD corneal antigen in several types of uveitis[59]. In 71% of 28 FU patients, a significant difference in cellular response was found compared to control groups (anterior, posterior and panuveitis) but not in terms of response. Similarly, Kruit et al demonstrated a high percentage of FU patients with serum antibodies against a 54 kD corneal epithelial protein[72]. The corneal epithelium has some antigens in common with the endothelium, where keratic precipitates are found in FU. Auto-immunity against corneal antigens could explain the keratic precipitates and their diffuse distribution[3, 67]. The significance of the detected auto-antibodies has yet to be elucidated. It could represent a primary or a secondary phenomenon. For the latter, two options have been suggested. Damage to the uveal tissue (due to infection) could result in an immune reaction against the altered tissue or it could reflect changes in permeability, which lead to increased accessibility to the immune system[13, 59]. Generalized tissue damage is atypical for a strictly auto-immune disease, in which usually specific cell types are attacked[1, 2]. Auto-immune disorders also generally exhibit strong HLA associations, which are absent in FU[73].

6. ETIOLOGY

Many speculations have been formulated concerning the etiology of FU. The atypical clinical presentation has prompted interest in this condition. It is puzzling that acute inflammatory signs, synechiae and CME are absent but long-term complications in the form of cataract and glaucoma do develop[74]. In the following pages, several of these theories will be presented. In addition, the most recent findings on the role of the rubella virus will be discussed.

6.1 FUCHS' THEORY

Fuchs assumed that a noxious agent of unknown nature was the cause of the disease and that it was active from the fetal or early postnatal period[5]. The agent would initially disturb the normal development of uveal pigmentation, which results in heterochromia. Subsequently, the eye would react with a mild, inflammation of long duration against this noxious factor. Cataract would develop due to changes in intraocular fluids, secondary to the iris pathology. Patients could also exhibit glaucoma, because of a block of the outflow channels by aqueous protein. Several objections have been formulated against Fuchs' hypothesis. Heterochromia was often acquired and the condition was mainly unilateral, whereas chronic uveitis is more often bilateral[13]. A common remark was the striking absence of inflammatory signs such as synechiae or photophobia. Several authors found it strange that such a mild inflammation could so often result in cataract[13]. This caused a change in focus: several authors began to question the inflammatory nature of FU and searched for associations with non inflammatory causes of iris depigmentation.

6.2 THE ORTHOSYMPATHETIC THEORIES

Theories concerning the influence of the orthosympathetic nervous system emerged from the observation that sympathetic lesions could lead to iris hypopigmentation. This is generally the consequence of an adrenergic dysfunction at a very early age, not in adults. It was suggested that impairment of the orthosympathicus would also cause the other signs in FU[13].

6.2.1 LESIONS OF TROPHIC FIBERS

Bistis claimed hypochromia associated with cataract could occur due to a trophic defect, which he would later connect with a sympathetic paralysis. He originally believed that trophic fibers accompanied the OS to the iris. A defect in these fibers would interrupt the process of the uveal pigmentation[67]. Adherents of this theory assumed that these trophic fibers could be damaged in several ways and that only the trophic fibers towards one eye would be harmed, without other signs. Bistis did not manage to obtain experimental evidence to support his theory. By surgically creating unilateral OS lesions in 4 rabbits, the clinical features of FU did not appear. The rabbits did develop heterochromia and one of them had some flare in the anterior

chamber but all other FU features were absent. No proof of the existence of trophic fibers accompanying the OS could be found either[8][13].

6.2.2 LESIONS OF THE ORTHOSYMPATHICUS

Iris hypochromia can occur in congenital Horner's syndrome. A common mechanism was suggested for the heterochromia in FU. Despite the very small number of patients with coexisting FU and Horner's syndrome, it was believed by some that these disorders had a linked pathogenesis. An impairment of the sympathetic nervous system would lead to an insufficient innervation of the stromal melanocytes, which would result in hypochromia in both Horner's syndrome and FU[8]. Vasodilatation with an increased capillary permeability would cause differences in the content of the aqueous[13]. These changes would then cause keratic precipitates, vitreous opacities, cataract and sometimes glaucoma. An adjusted version of this theory was that of a sympathetic paresis, rather than a paralysis. FU was not considered as an inflammatory but as a degenerative process[9].

Loewenfeld and Thompson, two neuro-ophthalmologists, formulated several arguments against these OS theories in their extensively documented papers (1973)[75]. Iris hypochromia can indeed result from a lesion of the OS innervation, but in later stages of life, pigmentation has already been completed. In cases of accidental, pathologic or surgical disruption of the OS, no change in eye colour has been described[13]. The epidemiology does not support this theory either: Loewenfeld and Thompson studied almost 1800 published FU cases and found 25 (1.4%) patients with both FU and Horner's syndrome[75]. This number did not suffice to support a causal link between a sympathetic defect and FU. In the IUSG study of Dernouchamps, potential sympathetic changes were only noticed in 3(0.5%) of the 550 FU patients[13]. Jones encountered no patient in his series of 103 FU patients with coexisting Horner's syndrome[30]. A third argument was the different appearance of an eye with sympathetic hypochromia and an FU eye. In sympathetic hypochromia, the eye does not show changes in texture or signs of inflammation. Next to reduced pigment and sometimes a slight hypoplasia of the anterior border layer of the stroma, the eye seems healthy[1, 75]. The affected eye may be paler, but the iris details remain sharp. OS lesions do not lead to the presence of inflammatory cells in the anterior chamber nor to a permanent permeability increase[13]. Pupillary changes cannot be fully explained either. In eyes with an OS lesion, the pupil at the affected side should be relatively smaller, because of the dominant cholinergic system. In FU however, both relative miosis and mydriasis are possible but slight mydriasis is more frequently reported, due to atrophy of the sphincter[3, 75]. These arguments, stressing the lack of similarities, have led authors to reject this association. However, possible OS elements within the pathophysiology of FU have been suggested in later studies. Since 1973, more reports on FU patients with Horner's syndrome have been published. Adrenergic dysfunction could account for the decrease in melanin content, as the stromal melanocytes have a direct OS innervation[67]. The increased permeability of the blood-aqueous barrier can be explained by a lack of OS tone but occlusion of iris vessels cannot be accounted for, which makes ischemia difficult to explain[1]. EM of iridectomy specimens has demonstrated degeneration of

the myelinated nerves with associated changes in melanosomes[3]. It seems more likely that the changes at nerve endings and melanocytes are secondary to chronic inflammation than that they reflect a primary (congenital) innervation defect that causes a faulty production of melanin granules[8, 19].

6.2.3 STATUS DYSRAPHICUS

Bremer (1926) introduced the concept status dysraphicus, a microform of syringomyelia[75]. While studying relatives of syringomyelia patients, he discovered a series of "syringomyelia-like stigmata", which he named status dysraphicus. This status represented a syndrome of dysmorphia and unilateral abnormalities, due to a faulty closure of the neural tube[8]. Pigmentary changes to the skin were attributed to deviations in the function or the distribution of the OS nerve system[1]. Passow was the first to apply this concept to ophthalmology, by studying Bremer's patients. In some patients sympathetic heterochromia was found. Therefore, FU and Horner's syndrome were considered to be part of this status. Passow believed FU to be an extensive type of sympathetic heterochromia. Other manifestations of this status dysraphicus were skeletal disorders such as kyphoscoliosis, Marfan syndrome and Parry-Romberg syndrome but sometimes, FU was the sole clinical feature[67]. By examining the spinal cord of status dysraphicus patients, attempts were made to discover histologic evidence for this theory. Franceschetti found 'dysraphic signs' in 45% of his FU patients but admitted that in all patients but one the signs were very mild[19]. Loewenfeld and Thompson critically reviewed the work of Bremer and Passow. They found great discrepancies between the histopathologic changes detected in the spinal cord and the clinical features of the patients. They stressed that no solid evidence was present for the existence of status dysraphicus[75]. It was created as a concept and the theory supporting it was never critically reviewed. Horner's syndrome and status dysraphicus are both associated with heterochromia but not with FU as such.

6.2.4 ASSOCIATION WITH THE SYNDROME OF PARRY-ROMBERG

Sugar and Banks associated the syndrome of Parry-Romberg with FU in 1964[76]. This syndrome, also referred to as hemifacial atrophy, is characterized by a progressive, unilateral atrophy of the face. The skin is affected first, followed by the subcutaneous fat, the muscles and even the underlying bone with subsequent facial malformation[67]. Sugar and Banks detected 13 patients with Parry-Romberg and FU by reviewing the literature since 1913 and added one patient of their own practice. They suggested that based on this association, both conditions had a common etiology. A defect in the OS nervous system would cause neurovascular or neurotrophic changes, which either resulted in Parry-Romberg or in FU[76]. In later studies, 4 additional patients with this association have been described[67]. Loewenfeld and Thompson formulated several remarks on this subject. Patients with FU and hemifacial atrophy did not show the typical clinical features of FU: they found pigmented keratic precipitates and sometimes posterior synechiae, but iris atrophy or heterochromia was absent. There was also doubt about a sympathetic lesion as the cause of Parry-Romberg[75]. Pupillary changes, Horner's syndrome and heterochromia can be the consequence of impaired OS innervation[67]. However, many patients with an OS lesion did not develop this syndrome. The intraocular

manifestations were more probably caused by the same inflammatory process affecting the face, than by a second disease. Jones also found 2 FU patients with coexisting hemifacial atrophy in his series of 103 patients[30]. The author claimed that Parry-Romberg may be one of the different etiologies of FU, as it is still unknown whether FU is a single pathologic entity with only one cause. Evidence is too incomplete to implicate this syndrome as a cause of FU.

6.3 INHERITANCE

The existence of two hereditary types of heterochromia – simple heterochromia and heterochromia in Waardenburg's syndrome – gave rise to a hypothesis of a hereditary ground for heterochromia in FU and for FU itself[13]. Even though these two entities have always been considered as distinctly different from FU, it led to the idea that all types of heterochromia were dominantly inherited. Both congenital and acquired heterochromia have been described in FU. If FU itself were a congenital disorder, it is to be expected that patients with congenital heterochromia would develop FU sooner than in acquired heterochromia[30]. This does not appear to be the case[77]. Few familial cases of FU have been published. Loewenfeld and Thompson found only 5 families with 2 FU cases in the same family and were unable to find a family with 3 or more FU patients[6]. Dernouchamps found 6 familial cases in 550 FU patients of his IUSG correspondents[13]. Liesegang observed 3 related sets of patients in his 54 FU patients in which 2 of the children had congenital heterochromia[18]. The number of patients in the same family seems too low for a direct inheritance, especially when considering that such cases are somewhat self-selective for publication[3]. The lack of epidemiological support has been attributed to a low penetrance of the gene[75]. Makley (1956) described a pair of monozygotic twins who both developed FU at the age of 43, within a time range of 6 months[78]. This case report does not exclude an intrauterine infection or a congenital anatomical failure, predisposing for FU[63]. Within the family of these twins, no other FU patients were found. Jones and Read also reported on twins but found discordance: only one of the monozygotic twins had FU[77]. They were also unable to find other FU members within the family, but they only looked for family members with a history of heterochromia or inflammatory eye conditions[67].

A hereditary basis was also suggested for disorders claimed to be associated with FU. Loewenfeld and Thompson extensively reviewed these assumptions, as authors suggested that due to the association with FU, FU would be hereditary as well[75]. Hereditary sympathetic heterochromia was claimed to exist, but it was the anomaly causing damage to the efferent OS (e.g. a cervical rib) that was hereditary. Status dysraphicus was also considered by some as heredodegenerative, but this only rested on aspecific "dysraphic signs" in family members of FU patients. These hypotheses were only based upon observation, without any solid evidence. FU has also been reported in association with the hereditary condition retinitis pigmentosa (RP)[8]. Chowers et al found a statistically significant higher percentage of FU patients in a group of RP patients

compared to a control group[79]. RP may be a risk factor for developing FU, but considering the low number of patients (1.2% of 338 patients), it is doubtful whether it truly is a clinically significant association.

The tiny minority of FU cases in the same family leaves the option of genetic factors affecting the risk of developing FU open. Studies on HLA-antigens (human leukocyte antigens) in FU patients have only showed minor deviations in the distribution of HLA-antigens compared to healthy control groups[67]. A statistically significant negative association with HLA-A2 was found in one study[67]. A decreased frequency of HLA-CW3 and HLA-DRW53 was also determined in FU patients compared to healthy controls but this was not highly significant[73]. Spriewald et al investigated the role for the CTLA4-gene (cytotoxic T cell antigen 4) in the susceptibility for FU[80]. CTLA4, expressed on the surface of T helper cells, transmits an inhibitory signal to T cells. Differences in allele frequency in FU patients compared to healthy controls were found. A recent study revealed that FU patients exhibit a significantly higher frequency of ICAM-1 G/R 241 polymorphism than healthy controls[81]. ICAM-1 (an adhesion molecule) plays a role in the recruitment of immune cells, but there is no general agreement on the functional differences of the various polymorphisms. These isolated findings could represent risk factors for FU, but publications with a larger number of patients are necessary to confirm this statement. None of these studies manage to offer sufficient and conclusive evidence. In retrospect, a hereditary character is highly unlikely: no solid evidence has been found to prove the hereditary theory in FU. Genetic predisposition cannot be excluded, this option therefore remains open.

6.4 VASCULAR THEORY

A vascular role in the development of FU has also been explored. The filiform hemorrhage during paracentesis and results from histologic and studies give support to a vascular pathomechanism[63]. Hyalinization of the iris vessel walls, partial and sectorial vessel occlusion have been observed in FU eyes[5]. Ischemia is capable of causing inflammation, the opposite seems less likely: inflammation generally results in hyperemia[82]. La Hey et al observed deposits of Ig and complement on the iris vessel wall in FU patients but were unable to demonstrate vascular inflammation using LM[67]. Immune complexes were also detected in the aqueous of FU patients[13, 67]. It was postulated that a complement-antibody mediated reaction could cause vasculitis of the iris vessels with subsequent ischemia. The ocular localization of the disease was explained by the presence of specific intraocular factors, which would cause intraocular formation and deposition of immune complexes[1]. The histologic findings are in conformity with this concept of an immune complex vasculitis, but there is not enough evidence to fully support it. No associations have been found with systemic disorders, whereas vasculitis is usually not isolated within one organ (mostly) unilaterally. Arguments in favour of this theory appear to rest on the interpretation of investigation results, not on solid evidence. Considering the recent etiologic findings on rubella virus, it is more likely that the encountered vascular abnormalies are a consequence of the inflammatory reaction, rather than the primary

trigger of FU. A hereditary vascular abnormality (such as a dysfunction of the OS iris innervation), representing an anatomical predisposition for FU, remains a possibility as it is difficult to exclude.

6.5 OCULAR TRAUMA

Ocular trauma has been described in the history of a small proportion of FU patients[11, 21, 83]. No evidence of intraocular damage following ocular trauma was discovered in such cases[3]. Saraux et al were convinced that FU was secondary to other ocular diseases or to trauma. Ocular trauma could explain the predominant unilaterality of FU[83]. The diffusely scattered keratic precipitates were explained by a hypersensitivity against corneal antigens triggered by previous trauma[11]. However, no convincing pathogenetic connection with ocular trauma has been determined. Only sporadically is ocular trauma mentioned in the history, without specifying the type of trauma. This unsupported theory should therefore be discarded.

6.6 INFECTIOUS AGENTS

Several previous theories such were based on the assumption that FU was not an inflammatory but rather a degenerative process, secondary to a primary disturbance. Fuchs however already found plasma cells in his iridectomy specimens and clearly stressed the inflammatory nature of the disease[5]. Later histologic studies have confirmed this immune activity, which has initiated the search for an infectious agent triggering this inflammatory response. The most recent findings point to an infectious trigger (rubella virus) causing a self-maintained inflammation.

6.6.1 TOXOPLASMA GONDII

Ernst Fuchs remarked lesions in the posterior segment of the eye in 2 of his 38 patients[5]. Some authors do not believe such lesions to be part of the clinical features of FU, but nevertheless, they are frequently reported in FU patients[23]. The reported prevalence of such lesions in FU is very variable, ranging from 3.8% to 65%[10, 24]. Several factors can attribute to variations in the reported percentages: the regional prevalence of T. gondii (which is shown by variable serologic values), the virulence of various T. gondii species, the examination methods, the type of study and the diagnostic criteria, for both FU and the lesions[67]. Retrospective reports point to far lower numbers, such as Liesegang (3.7%) and Arffa and Schlaegel (7.5%)[18, 84]. Kimura et al remarked that in FU, the peripheral retina is seldom examined[9]. Cataract, a frequent complication in FU, also makes visualization of the peripheral retina difficult[2]. Due to the retrospective nature of a study, it remains unknown whether careful examination of the retina would have revealed more lesions. Some authors fail to mention their definition of a "toxoplasmosis-like scar"[67]. Not only toxoplasmosis-like scars have been reported in FU, also other types such as scars characteristic of Toxocara and histoplasmosis have been described[3]. Due to these variables, it is highly important that a control group of the same population and region is studied simultaneously , which was not the case in many reports[67]. In studies with control patients, the mean prevalence of chorioretinal scars consistent with

toxoplasmosis was significantly higher in FU patients than in control groups[22, 24]. Studies on the prevalence of chorioretinal scars in a general population and in a retinal clinic have demonstrated scars in 0.6% and 4% respectively1[3]4. Such results have caused speculation on an etiologic relationship between T.gondii and FU.

Several theories have been formulated in an attempt to explain the coinciding of chorioretinal scars and FU. In the very beginning, tuberculosis was claimed to be responsible for these lesions. This led to the hypothesis of a correlation between tuberculosis and FU. However, FU did not follow the decrease in incidence of tuberculosis. Authors eventually had to conclude that the cases with tuberculosis and FU were more than likely based on coincidence and that there was no causal relationship. In 1923, Janku showed that Toxoplasma gondii could cause chorioretinitis and chorioretinal scars, which was confirmed in later reports[85]. This offers an explanation to why Ernst Fuchs and authors shortly following him did not consider T. gondii as a possible cause of chorioretinal involvement.

de Abreu et al (1982) considered a (previous) T. gondii infection responsible for the scars in FU. In 13 of their 23 FU patients lesions were found with a positive serum IF reaction for T. gondii in all 13 patients. No control group was used to compare the incidence of toxoplasmosis-like scars or the serologic values with and no other types of retinal lesions were described. The authors believed that T. gondii would cause sensitization of a retinal antigen, which would give rise to FU in an autoimmune way[40]. Saraux et al also encountered chorioretinal lesions in a high percentage of FU patients (60%), with serologic confirmation of a T. gondii infection in all patients. Additionally, the aqueous of 3 of these patients was examined and in all of them, a positive Goldmann-Witmer Coefficient (GWC) for T. gondii was determined. The authors even suggested that all diseases that cause destruction of the retina could induce FU[83]. Observations do not consistently support a direct etiologic hypothesis for T. gondii. If the pathway through autosensitization were to exist, highly specific conditions would have to be present as FU is not a common disorder[3]. Primarily, the high frequency of toxoplasma chorioretinitis in these countries (Brazil and France) requires a control group in order to obtain objective data. Only sporadically, FU patients with active lesions in the FU eye have been described. A case report of a patient with congenital ocular toxoplasmosis who developed unilateral FU has been published[67]. Also, the chorioretinal scars do not exclusively appear in the FU eye. Several combinations have been described in literature: unilateral FU and bilateral scars, bilateral FU and unilateral scars or even scars in the contralateral eye but not in the FU eye[67]. Dernouchamps suggested two explanations for the lesions: they could be secondary to the agent causing the iridocyclitis or to a deviated immunological response or they could favor FU development[13]. The seropositivity for T. gondii also varies, in some areas, it is almost universal in adults. Vadot found chorioretinal scars in 27% of his patients, in which no specific topography was recognized. Contrary to other reports, serologic values were available for all 45 FU patients. 62% seropositivity does not substantially differ from the general population[11]. La Hey et al found no serological differences between three subgroups of FU patients: the ones with toxoplasmosis-like (9 patients; 10.2%) or aspecific scars (11 patients; 12.5%) or without scars (68 patients; 77.3%). An

association was found between FU and toxoplasmosis-like scars, but not between FU and toxoplasmosis itself. Serologic testing and investigations of cellular immunity were unable to demonstrate an underlying association. Analysis of aqueous humour samples on toxoplasma antibodies was also non-significant[86]. In several series, patients with chorioretinal scars showed negative serology on non-diluted serum[21, 22, 84]. A negative toxoplasma serology on non-diluted serum in adults makes ocular toxoplasmosis highly unlikely. Inversely, positive serology is not conclusive for ocular toxoplasmosis, as demonstrated by the high prevalence of positive titres in the general population[67].

Schwab had a different vision on the matter. He also found a high percentage of scars in his FU cohort (16/25 patients) but in 5 of these, the typical keratic precipitates were absent. Schwab believed ocular toxoplasmosis could create a similar clinical spectrum as FU, but that these diseases did not share a common pathogenesis. Anterior uvea activity could cause subtle changes such as heterochromia and low-grade inflammation with fine keratic precipitates and mimic the image of FU[85]. Ocular toxoplasmosis may be able to cause some clinical features of FU, so that it could be perceived as FU. Further investigation is necessary to discover whether patients with a diagnosis of ocular toxoplasmosis show the clinical features of FU in the anterior segment.

Another approach was proposed by Arffa and Schlaegel, in order to explain the observed discrepancy between the presence of fundus lesions and negative toxoplasma titers. They additionally determined lesions in 12 out of 67 patients that did not resemble toxoplasmosis. These authors suggested that the lesions would result from autoimmunity against retinal or choroidal antigens[84]. These chorioretinal scars represented retinal inflammation related to the anterior segment involvement. La Hey et al found a positive cellular autoimmune response against retinal S-antigens at significantly higher percentages in FU compared to the control group of healthy patients or patients with anterior uveitis[87]. This finding was inconsistent: positive immune responses were also found in patients lacking chorioretinal scars[67]. This makes it highly doubtful that immunization against S antigen would cause the lesions in FU. These S-antigens have also been studied in regard to ocular toxoplasmosis. Abrahams and Gregerson (1982) discovered high values of S-antigen antibodies during the acute stage of the disease. Titers seemed to follow the clinic: as the clinical activity declined, lower titers were found[88]. Saraux et al raised the possibility of the production of antibodies in the course of ocular toxoplasmosis which can crossreact with uveal antigens at a later stage. FU was considered a secondary phenomenon of autoimmune nature: an initial infection or other trigger could cause sensitization of retinal autoantigens, which evolved in a mild autoimmune uveitis[83]. Experimental models of uveitis caused by retinal antigens however showed a very destructive type of uveitis[3].

The discrepancies in the association chorioretinal scars – ocular toxoplasmosis – FU have strongly diminished the assumption of an etiologic role for T. gondii in FU. Some authors do not exclude that in exceptional cases, a T. gondii infection, congenital or acquired, could cause FU[3, 22, 24]. In this statement, they

refer to the sporadic FU cases with active T. gondii lesions or a history of congenital toxoplasmosis. The data is insufficient to consider T. gondii as a major etiologic factor, but the clinical association remains remarkable and poorly understood.

6.6.2 Herpes Simplex Virus (HSV)

In 2000, HSV was implicated in the pathogenesis of FU. Barequet et al published a case report of a FU patient with a positive PCR for HSV DNA in the aqueous humour. No VZV or CMV DNA was detected, intraocular antibody analysis was not performed[89]. Other studies were unable to detect HSV DNA or anti-HSV antibodies in FU patients[90-92]. Ruokonen et al detected anti-HSV antibodies in a subset of FU patients, but these titers were markedly less elevated than the anti-rubella antibodies (cf. Infra)[92]. Therefore, it is less likely that the isolated finding of Barequet et al is truly significant.

6.6.3 Cytomegalovirus (CMV)

Chee and Jap found a positive PCR reaction on CMV DNA in 15 of their 36 FU patients (41.7%). They discovered significant differences in age at diagnosis, gender and prevalence of nodular keratic precipitates between CMV positive and negative FU patients as well. PCR on rubella genome or antibody detection were not performed[93]. As in the case of HSV, this is the sole report indicating some kind of connection between CMV infection and FU. The high proportion of positive PCR results however remains remarkable. The diagnostic criteria for FU were quite broad: chronic, asymptomatic mild inflammation with diffuse characteristic stellate KPs and no posterior synechiae, with possible diffuse iris atrophy and vitreous cells. This is reflected in the mean age at diagnosis of CMV positive eyes (65.3%), which is markedly higher than generally reported in FU patients. It is therefore possible that the presumed FU patients were not all true FU patients.

6.6.4 Rubella virus (RV)

6.6.4.1 Reports on the association FU-RV

Jones concluded his work on FU in 1993 with the words “perhaps a review another 20 years from now may provide all the answers”[3]. The recent breakthrough in identifying the etiologic agent may prove this speculation right. Quentin and Reiber (2004) were the first authors to report the occurrence of anti-rubella antibodies in the aqueous of FU eyes. They have determined the immunoreactivity against several organisms (herpes simplex, varicella zoster, measles, rubella and T. gondii) in the aqueous humour of 52 FU patients and 155 patients with other types of chronic uveitis, MS or senile cataract. A positive result consisted of an AI (antibody index) above 1.5. This antibody index, a modification of the linear Goldman-Witmer Coefficient (GWC), reflects the specific, intraocularly synthesized antibodies. An increased AI against rubella was found in all 52 FU cases, with a median value of 20.6. The aqueous of 11 MS patients also showed evidence of intraocular production of anti-rubella antibodies but at significantly lower AI values (median value of 3.0). An elevated AI was not seen in any of the control patients, in MS it is part of a

polyclonal response. Additionally, PCR was used on 28 FU samples and 22 control samples (senile cataract) in order to detect the rubella genome. Each control sample had a negative PCR result, whereas 5 FU samples (15%) showed positive results[90]. Remarkably, these patients were all younger than 40, which may suggest a limited period of viral persistence.

De Groot-Mijnes et al similarly studied the intraocular antibody production in 14 FU patients and 32 control subjects. In 13 FU patients, a positive GWC was found against RV. One FU patient had a lower GWC but showed a severe blood-aqueous barrier breakdown. None of the 32 controls had a positive GWC for RV and none of the FU patients showed significant antibody production against other micro-organisms (HSV, VZV or T. gondii)[91]. Unfortunately, in both this publication and the first mentioned report, no information was available on rubella infection in the past or on the vaccination status of the FU patients.

Birnbaum et al later published an epidemiological observational case study on the subject of FU patients and rubella vaccination. 131 (3.4%) of the patients seen at an American uveitis clinic between 1985 and 2005 were diagnosed with FU. These patients were divided into groups based on date of birth, ranging from 1919-1928 to 1989-1998. A trend analysis was performed and the results were compared with those of idiopathic decrease was observed in the number of FU patients, whereas the incidence of ICI and ICGC did not substantially change over time. The most marked decrease was seen between the periods 1969-1978 and 1979-1988, which correlated with the implementation of the US rubella vaccination program in 1969. Oddly so, a decrease was already seen in patients born in the previous decade (1959-1968)[94]. The authors explained this observation as followed: initially, children from 1 year old to puberty were vaccinated, which covers all patients born after 1957. This could explain the observed decrease as most cases of rubella occur before the age of 11. Only a small number (4 patients born after 1979) of patients were recently diagnosed with FU. However, FU mostly presents in the third or fourth decade. Patients born after 1979 were 26 years old or less at the end of this study. This was also the case for the control group, since the age of presentation in ICI and ICGI is similar to that in FU. Therefore, the difference between these entities and FU cannot be solely explained by an age-related trend. The authors also investigated the difference in incidence between US-born and foreign-born patients. A relative increase of foreign-born FU patients was observed, but this was not seen in ICI and ICGI. A few confounding factors must be kept in mind. It should not be assumed that all children were vaccinated: vaccination is recommended for all children but is not obligatory. There is also some uncertainty about the longterm level of immunity against rubella virus after vaccination. These results were based on 1 tertiary center, which is why generalizing these results requires caution. Norrsell and Sjödell also mentioned that the relative proportion of foreign-born patients (more specifically Iran, Jordan, Lebanon and Bosnia) was higher in their FU patients than in the general Swedish population[22]. They however deemed it inappropriate to formulate conclusions based on the small number of patients studied.

Ruokonen et al determined the intraocular antibody production against RV, CMV, HSV, VZV and T. gondii in 63 FU patients. Immunoreactivity against RV was present in every FU patient and absent in each control patient. PCR was positive for rubella genome in 2 of the 20 tested FU samples (10%). Interestingly, one of these patients was HIV-1 positive. 9 out of 63 FU patients also showed antibody production against other viral antigens (mainly HSV) but at far lower intensity[92]. Simultaneous infection with these viruses was suggested but the lack of response to antiviral therapy and negative PCR results on viral genomes did not support this hypothesis. In some FU patients, a costimulation of B lymphocytes could arise and lead to the production of antibodies against other antigens. A survey on rubella vaccination was included in this report. Only 1 FU patient claimed to have received vaccination, which supports the hypothesis of RV as the etiology of FU.

Following three reports on European populations, a recent Japanese study resulted in similar conclusions. A positive GWC was detected in 10 out of 14 FU patients. The remaining 4 patients had inadequate AH samples, which rendered the GWC calculation impossible. However, they were able to detect anti-rubella antibodies in the AH of these 4 FU patients. One vitreous sample was also examined and exhibited a high GWC. The rubella genome was detected in 2 out of 9 AH samples with RT-PCR. Additionally, the 14 FU patients claimed not to have received rubella vaccination and 11 of them confirmed a history of rubella infection (not mentioned at what age). In 1 FU patient, rubella virus was isolated from the AH[95]. Unfortunately, no specific information was offered on the type of infection: whether it was congenital or acquired, or at what age it was contracted. Only anti-rubella antibodies were tested, no antibodies against other micro-organisms. The results of 4 case-control studies on rubella-specific antibodies are listed in table 3.

TABLE 3: RESULTS OF INTRAOCULAR ANTIBODY DETECTION IN FU PATIENTS

Study	Quentin and Reiber	De Groot-Mijnes et al	Suzuki et al	Ruokonen et al
Number of FU patients	52	14	14	63
Number of controls	155	32	8	46
Control group	Cataract, MS, anterior uveitis, VZV iritis, HSV iritis, toxoplasmosis	Herpetic anterior uveitis, ocular toxoplasmosis	Sarcoidosis, Posner-Schlossman syndrome, HSV iritis, Behcet disease, unclassified uveitis	HSV- and VZV-associated uveitis, HLA B-27 positive anterior uveitis, Posner-Schlossman syndrome
Type of index used	Antibody Index (AI ≥ 1.5)	Goldmann-Witmer Coefficient (GWC > 3)	Goldmann-Witmer Coefficient (GWC > 3)	Antibody Index
Tested organisms	RV, VZV,HSV, T.gondii	RV, VZV, HSV, T.gondii	-	RV, CMV, HSV, VZV, T.gondii
Rubella-Ab in FU patients	52/52 (100%)	13/14 (93%)	10/10 (100%)*	63/63 (100%)
Rubella-Ab in control group	11/15 MS patients (73%); 0/140 others	0/32 (0%)	0/8 (0%)	0/46 (0%)
Rubella genome	5/28 (18%)	-	2/9 (22.2%)	2/20 (10%)
Median age of FU group	43 (16-73)	42 (23-73)	48.5 (27-62)	46.9 (12-86)
Vaccination status	-	None vaccinated	None vaccinated, 1 uncertain	1 vaccinated, 1 unknown, 61 not vaccinated
History of rubella infection	-	-	11/14 (78.6%)	-

* AH samples of 4 FU patients were inadequate, GWC could not be determined.

Siemerink et al published a case report of a 13-year-old boy with FU who underwent a diagnostic aqueous humour tap. The sample was searched for antibodies against HSV, VZV, T. gondii and RV. Results were negative, except for a positive GWC for RV. The boy had not been vaccinated against rubella virus, but the parents could not recall a rubella infection[96]. De Groot-Mijnes et al reported on 2 FU patients (26 and 29 years of age) who also exhibited a negative GWC for HSV, VZV and T. gondii, but a positive GWC for RV. No viral RNA or DNA could be detected in the two samples. In both patients, two sequential samples (19 and 8 months after the first tap) showed an elevated GWC. The second patient had not been vaccinated and showed a substantially higher GWC than the first patient (132.79 compared to 15.01 on first sample)[28]. These reports further indicate an association between FU and RV, but do not offer any valid evidence for the power of the association or the validity of diagnostic laboratory testing.

De Visser et al approached the observed association FU-RV from a different perspective. In a retrospective case-control study, they compared a group consisting of 30 patients with a positive GWC and/or PCR for RV with 13 control patients (chronic idiopathic anterior uveitis with a low GWC for RV). The objective was to compare the clinical spectrum of these RV positive patients with the features of FU. The principal FU criteria applied in this study were: 1) keratic precipitates;2) diffuse iris atrophy and/or heterochromia;3) absence of posterior synechiae; and 4) cataract. The clinical spectrum of RV positive patients was indeed similar to that of FU. Additionally, 15% of the RV negative patients also exhibited all four FU criteria[97]. The authors claimed that this could imply a different etiology in a subset of FU patients, other than rubella virus. There are however no standardized diagnostic criteria for FU. Therefore, the four criteria used in this study are not absolute: the choice of criteria may have influenced the results. Vitreous involvement or the absence of posterior synechiae for example are possible criteria, but were not included. The retrospective nature of this study may have lead to bias: the exact prevalence of some features can be difficult to determine. Information on past rubella infection or vaccination was also absent.

6.6.4.2 Characteristics of Rubella virus

Rubella virus, an RNA virus of the Togaviridae family, can cause both a congenital or acquired infection[98]. Acquired rubella (also called 'German measles') was first characterized as a benign self-limited disease with erythematous rash, fever, lymfadenopathy and arthralgia[99]. Rubella virus (RV) invades the respiratory epithelium of the nasopharynx, replicates in the reticuloendothelial system and causes a secondary viremia. Gregg discovered the teratogenous effects, which was the first observation of teratogenicity by a viral agent[98]. Subsequent clinical reports confirmed the relationship between congenital defects and maternal rubella infection. The congenital rubella syndrome (CRS) has a wide range of severe systemic complications with a classical multiorgan triad of cataract, cardiac defects and deafness. Ocular complications are very common, reported in 43% to 78% of CRS patients[99]. The broad clinical spectrum follows from the uneven distribution of foci of infected cells, the variable number of infected cells and from an non-simultaneous

infection of the affected tissues. An infected mother may undergo a very mild, insignificant flulike condition. Occasionally, the clinical picture is more severe with vascular thrombosis, encephalitis, myelitis and optic neuritis[100]. The timing of maternal infection determines the severity of the disease because of the link with the maturation of the fetal host mechanisms. When RV is contracted in the first 8 weeks, 1 out of 2 results in a fetal infection. This decreases in subsequent weeks to less than 10% at week 16[99]. Viral infected cells have a slower replication, to about half the normal rate[100]. If a fetus is unable to eliminate the agent, a chronic infection or immune tolerance can develop. A similar trend exists for the occurrence of congenital defects: infection in the first 11 weeks leads to defects in 100% of the cases, whereas no congenital defects usually arise from infection after week 20[98]. The result can be devastating in case of an early infection, especially during organogenesis. Prior to the development of an effective vaccine, the last worldwide rubella epidemic occurred from 1963 to 1965. In this period, an estimated 10% of childbearing women contracted the infection and up to 30% of their neonates developed CRS[99]. This implies that approximately 70% of the infants with congenital rubella were asymptomatic at birth. In developed countries, the MMR (measles, mumps and rubella) vaccine has reduced rubella to a very rare disease but in developing countries, it remains an important cause of blindness[98]. The purpose of vaccination is to prevent CRS by providing women at childbearing age with rubella immunity. The transmission of rubella virus can only be prevented when high coverage rates are established. Low coverage can increase the incidence of CRS on a longer term[101].

6.6.4.3 OCULAR RV MANIFESTATIONS

Acquired rubella infection is not known to be associated with ocular involvement. CRS has a wide range of possible ocular features. Several of these, such as dacryostenosis, corneal edema, keratoconus, posterior synechiae, primary atrophy, microphtalmos and others, are not encountered in FU[98]. This goes to show how widespread the ocular consequences of a fetal rubella infection are. The iris can be hypoplastic, if the infection is contracted early in pregnancy. Chronic, granulomatous iridocyclitis has also been described in which the iris pigment epithelium undergoes focal necrosis and vacuolization. Infection in the first trimester can also result in nuclear cataract and viral persistence in the lens for several years has also been reported[98]. A cataractous lens, next to the lymphoreticular system, is the body part where the virus can most often be recovered from[100].

In about 10% of CRS children, glaucoma has been described. This appears to have several possible causes: abnormal development of the angle, chronic iridocyclitis or cataract[98]. Retinal abnormalities are typical for CRS and in FU, chorioretinal scars of unknown significance are often described. However, other than the localization, these two types have little in common: the focal atrophy does not at all resemble the salt-and-pepper retinopathy of CRS, which is usually present in both eyes, contrary to FU[74]. Histopathologically, there are some similarities: depigmentation of the retinal pigment epithelium, without inflammatory activity[98]. Interestingly, some defects continue to evolve later on in life and there are also late

manifestations of CRS, such as diabetes mellitus (20% at 35 years old). Givens et al claimed "congenital rubella should be viewed as a chronic infection capable of producing progressive damage"[99]. Some of these late features are ocular: keratic precipitates, chronic uveitis, iris atrophy, cataract and glaucoma have all been described in CRS patients and may represent cases of FU that have been unreported in the past[74, 99]. These delayed signs are believed to be the result of either virus persistence or of (auto)immune processes, similar to suggestions for the etiopathogenesis of FU.

6.6.4.4 ETIOPATHOGENESIS

The laboratory results offer objective data on potential etiologic agents but fail to give insight into the exact pathogenesis. The nature of the relationship between FU and rubella virus is still enigmatic. Immunologic studies in FU have demonstrated oligoclonal IgG1 and predominant CD8+ T cells of a clonal nature in the aqueous, pointing to a slowly progressive, chronic B cell mediated disease[64, 102]. CD8+ T cells are known to respond to intracellular pathogens such as viruses. The antigen triggering this response could be the rubella virus. The odds ratio (OR) gives an idea of how strong an association is, in this case between the intraocular presence of anti-rubella antibodies and FU. It indicates how many times more likely FU is present in persons exhibiting high values of rubella-specific antibodies compared to those without. The ORs were calculated for the results of 4 case-control studies (cf. Table 4). These OR appear to be very high (infinite), pointing to a very strong association.

An acquired rubella infection may seem the most plausible but an in utero infection, less likely at first sight, is certainly possible. Infection past the first trimester could lead to the intraocular presence of RV without obvious clinical symptoms at birth. It is possible that in such children, delayed ocular manifestations can lead to the clinical features of FU. Rubella-specific Ab have been detected in children with a subclinical CRS at birth[74, 98]. It is remarkable how this hypothesis of an in utero rubella infection resembles the original thoughts of Ernst Fuchs. He assumed that the etiologic agent was present during embryologic or early postnatal life. Even though his concept was based on a completely different aspect (i.e. the occurrence of congenital heterochromia), it appears that the recent findings may fit his original idea. The pathogenetic pathway originally formulated for T. gondii as etiologic agent, can also be applied to RV. It was said that the agent would migrate into the ocular tissue in utero. It would then alter this tissue, causing the release of potent ocular antigens. Sensitization against such antigens could then lead to low-grade inflammation[67]. Some immunologic findings support this hypothesis. Auto-immunity against corneal antigens and retinal S-antigen has been demonstrated in FU patients (cf. supra). Destruction of iris tissue could alter the production of TGF-β and neuropeptides important for ACAID. It has been proved that poor immunoregulation can lead to the development of uveitis[103]. An acquired infection is another possibility. Chronic, latent or re-infections with RV are generally considered to be very rare as RV usually causes an acute infection[74]. The insidious onset and chronic course of FU may be the result of specific viral properties and/or of a disturbed immune

response. In case of an acquired RV infection, it is odd that RV, which reaches the bloodstream through the respiratory epithelium, would manage to reach the immune privileged tissue of the eye.

A third option is RV vaccination as a cause of FU. Transient conjunctivitis and uveitis have been reported following vaccination but the clinical features did not resemble FU. A case report of 2 patients revealed redness, pain and injection in all 4 eyes, 4 and 6 weeks respectively following MMR vaccination[104]. Rubella genome was identified in these eyes by PCR[14]. Viral antigens of the live attenuated vaccine could induce immune activity by antigen mimicry, similar to inflammation induced by bacterial products[104]. The observation of Norrsell and Sjödell that 6 of their FU patients had been vaccinated at the age of 13 could imply the induction of FU by the vaccin[22]. However, it is also possible that these patients had a subclinical rubella infection prior to vaccination. The epidemiological findings of Birnbaum et al contradict this third concept: a trend towards a higher prevalence would be expected, but instead, a decrease was observed[94].

The resulting inflammatory activity is also quite enigmatic. Is it comparable to the mechanism in acute glomerulonephritis following angina or reactive arthritis, in which the cross-reaction is self-limited? The mainly unilateral nature of FU (in about 90% of the cases) remains puzzling. What are the defining factors that determine which eye is affected? Why does the infection give rise to such a local reaction? When the infection is contracted, it is possible that the ocular immunity is capable of preventing the spread of infection so that it remains local. Unilateral FU cases have indeed never been reported to become bilateral. The host defenses may be unable to fully eliminate the virus, which leads to a persisting inflammatory activity. One of the best studied examples of such a persistent viral infection is subacute sclerosing panencephalitis (SSPE), in which the measles virus causes a progressive neurologic disease. Both the measles virus and the brain cells are believed to be involved in virus persistence. Several mutations in the viral genome of SSPE virus make it distinctly different from the wild-type measles virus[105]. These mutations mainly result in a decreased expression of envelope proteins. It would be interesting to investigate the rubella genome found in the aqueous of FU eyes for possible mutations. Certain genotypes of RV may be associated with a higher risk of developing FU. Some of these genotypes are known to be geographically restricted: the observed variations in clinical spectrum may be the result of different genotypes triggering FU. The characteristics of the cell determine whether a lytic infection or an immediate persistent infection develops. The course of FU and SSPE is similar: a slowly progressive disease due to viral infection. However, there are some distinct differences. In SSPE infected brain cells, inclusion bodies consisting of viral particles have been demonstrated using EM[105]. No such evidence of intracellular viral persistence in ocular tissue has been provided in FU. SSPE is mainly a childhood disease, whereas FU mostly manifests in the third or fourth decade. Measles virus genome was detected in SSPE brain tissue, even after the brain tissue had been stored frozen for 27 years[105]. PCR detection of rubella genome demonstrates the presence of RV in 18%, 22.2% and 10% of the tested FU samples, respectively[90, 92, 95]. This corresponds with an average of 15.8% (9 out of 57 tested patients). It may be possible that PCR is not sensitive enough in order to detect very small amounts

of rubella virus. Effective treatment is not available for SSPE, immunization is the best prevention strategy. Epidemiological evidence supports a similar situation for FU. Administrating the measles vaccine was ineffective at changing the course of the disease, it would be interesting to observe the effect of vaccination on FU patients. The measles virus remains sequestered in the brain cells, but in which cells would RV then persist? The risk at development of SSPE seems higher when a measles infection is contracted before the age of 2. It may be possible that the immaturity of the immune system is involved in this persistence.

A second option is that rubella infection is contracted and gives rise to a cell-mediated immune reaction with the local production of rubella-specific antibodies that cross-react with the uveal tissue. This seems to be the main hypothesis at the moment: FU as an immunogenetically determined autoimmune disease, triggered by (predominantly or exclusively?) rubella virus. Similarities are striking with spondyloarthropathies, inflammatory joint diseases associated with HLA-B27, in which a highly similar concept is suggested. In FU, the infectious trigger is known but no genetic predisposition has been demonstrated. There may be a genetically determined immune dysfunction against RV in FU patients. Spondyloarthropathies have a known association with HLA-B27 (with typical acute anterior uveitis episodes), but the infectious trigger is not fully determined. The different distribution is highly interesting: a systemic rheumatic disease versus a mostly monocular disease. In this comparison, it is useful to consider the peculiar immunologic properties of the eye. The anterior chamber is an immune privileged site, because of the blood-ocular barrier in the tissue surrounding the anterior chamber. The intraocular microenvironment has anti-inflammatory and immunosuppressive properties, which leads to unexpected immune responses in order to protect the visual axis[104]. When this immune privilege is lost, severe damage to the eye can occur (due to infection and to auto-immunity to ocular antigens). The parenchymal cells of the iris and ciliary body secrete TGF-β, which inhibits antigen-driven T cell activation. It is possible that a decreased ACAID function is present in FU. It has been postulated that iris atrophy could cause a decreased concentration of TGF-β[67]. This would imply that the inflammatory activity, resulting from the disturbance of the benign micro-environment, is secondary to iris atrophy in FU, even though the opposite seems more likely. Further investigations are necessary to replace speculations with facts. Some aspects of FU, such as the Amsler sign and iris ischemia remain difficult to link to RV. Additional information on the history of rubella infection and the age at which the diseases (rubella and FU) have manifested would be interesting to further explore the etiopathogenesis (cf. figure 1 for current concept). In a subset of patients, the RV genome was present in the AH. More data on the immunologic status of these FU patients would be welcome. Investigations on the genetic background could offer support to the concept of genetically determined immune responsiveness as part of the initial pathogenesis. For the moment, this is merely a theoretical concept as no solid genetic association has been demonstrated.

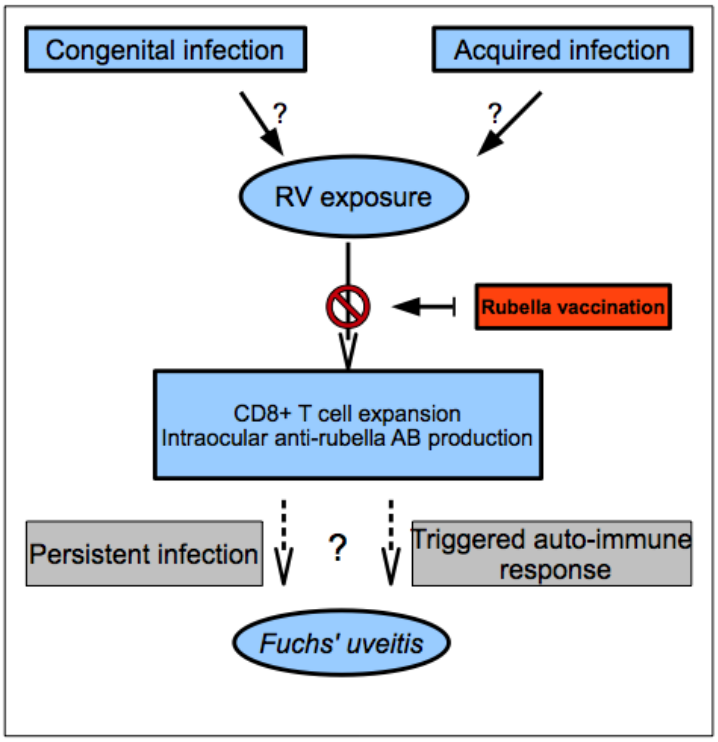

Figure 1: Current concept of etiopathogenesis of FU. It is still uncertain whether a congenital or an acquired infection is responsible for RV exposure. Vaccination programs have proved to cause a decrease in incidence of FU. The exact pathogenetic mechanism remains enigmatic.

6.6.4.5 RV THE SOLE ETIOLOGIC AGENT?

Several authors have mentioned belief in the concept of FU as a common clinical endpoint, with several possible triggers leading to this entity[64, 67]. A particular, unusual ocular response would cause the clinical entity of FU. Reported variations in clinical patterns could then reflect the etiology of FU in different populations, as the predominant cause would depend upon the seroprevalence within the population[20]. The sensitivity and specificity of anti-rubella antibody detection does not seem to support this idea: the number of false negatives appears to be limited (cf. table 3). These multiple etiologies would correspond to a certain number of false negative results, as a different etiology would lead to FU but not to the production of anti-rubella antibodies. Other viruses, such as HSV and CMV have been associated with FU but the evidence is very limited: results were based on significantly smaller patient groups and were not consistent in other reports, which contrasts with the findings on RV. The report on CMV DNA in the aqueous of presumed FU patients is particularly remarkable. In 41.7% of 36 FU eyes, CMV DNA was found in the aqueous, which is even higher than in RV (about 15%). Presumed FU patients older than 57 were 16 times more likely to have a positive PCR result[93]. This contrasts with the observation of Quentin and Reiber that RV genome positive patients were all younger than 40. It is quite puzzling whether this result has any significance, as anti-CMV antibodies were not significantly increased in any of the above mentioned studies. Is it possible to exclude other viruses as the etiologic agent of FU? Maybe not quite, as it is very difficult to prove that other viruses aren't able to generate FU in a small minority of the patients. The consistent laboratory results on RV make this less plausible than previously assumed.

6.6.4.6 MANAGEMENT

Next to a better understanding of the etiology, the results also have consequences towards diagnostics and towards management. Effective treatment for rubella infection is not available, there is only supportive therapy[98]. Viral etiology offers a rational basis for cessation of CS therapy. The observed decrease of FU since the implementation of the US rubella vaccination program may imply that FU could be extinguished through vaccination. Vaccination has been mentioned in relation with FU through two distinctly different perspectives. On one hand, it has been suggested as a possible cause but on the other hand, epidemiological data suggests that vaccination may prevent the development of FU. There is little data to support a causative relationship, but a protective role surely is possible. A study on rubella immunity after the standard vaccination regimen (14-18 months and 6 years) showed that 31% had a low Ab level at 15 year follow-up (lower than the suggested protective level)[106]. This would imply that almost one-third may be insufficiently protected at childbearing age, which leaves the possibility for an acquired infection at a later age.

6.6.4.7 DIAGNOSTICS

TABLE 4: CHARACTERISTICS OF INTRAOCULAR ANTIBODY DETECTION

	Quentin and Reiber	De Groot-Mijnes et al.	Suzuki et al.	Ruokonen et al.
Odds Ratio (95% CI)	Inf* (166.77-Inf)	Inf (54.76-Inf)	Inf (21.70-Inf)	Inf (785.56-Inf)
Sensitivity	100%	92.9%	100%	100%
Specificity	92.9%	100%	100%	100%
Positive Predictive Value	0.83	1.0	1.0	1.0
Negative Predictive Value	1.0	0.97	1.0	1.0
Positive Likelihood Ratio (95% CI)	14.09 (10.46-14.09)	Inf (12.54-Inf)	Inf (4.27-Inf)	Inf (24.09-Inf)
Negative Likelihood Ratio (95% CI)	0.00 (0.00-0.06)	0.07 (0.07-0.23)	0.00 (0.00-0.20)	0.00 (0.00-0.03)

* Inf: infinite

At present, 4 studies have been published on the determination of intraocular anti-rubella antibodies in FU patients. The consistent results suggest that the detection of these specific Ab could function as a laboratory confirmation of FU. Clustering the results of the various reports offers the opportunity to assess Ab detection as a diagnostic tool. In the assessment of a new diagnostic test, it needs to be checked whether or not the reference standard used in the studies were sufficiently accurate. Comparison of the clinical criteria for diagnosis of FU shows that only one study clearly summarized a number of criteria of which at least 4 out of 5 needed to be present. In the other three studies, only a description of how diagnosis of FU is usually made, was offered, without much further specification. Samples were also obtained in two different settings: during surgery for secondary glaucoma/cataract or by paracentesis. Samples obtained during surgery may represent a more advanced stage of the disease, considering the presence of complications. Both the antibody index and the Goldmann-Witmer Index have been used in order to determine the intraocular location of antibody production. The AI, an adjusted form of the GWC, could have the advantage that a disruption of the blood-aqueous barrier leads to less false interpretations. The sensitivity, specificity and likelihood ratio were calculated for the results of each of the 4 papers (cf. Table 4). In the report of Quentin and Reiber, the specificity was lower due to the positive results in several MS patients. However, MS does not cause problems for differential diagnosis. The predictive values are also listed, but these are less useful as they are affected by the prevalence of the disease. The likelihood ratio's (+LR and -LR) show the probability of the disease in case of a positive result (+LR) and the probability of absence of the disease when the result is negative (-LR). The results demonstrate very high +LR: in 3 out of 4 studies, the +LR is even infinite. It therefore appears that the antibody detection is reliable in differentiating FU from non-FU patients. PCR seems to be less useful for diagnostic purposes, due to its low sensitivity. The decision whether or not to perform the test is partly based upon its accuracy but also upon the influence of the result on the management of the patient. Determining the diagnosis of FU can protect a patient from unnecessary CS treatment and its potential complications. It can also avoid misleading expectations.

An additional consideration is the diagnostic procedure necessary to obtain an aqueous sample. This is an invasive diagnostic method (an aqueous humour tap). It is generally considered a safe procedure. Van der Lelij and Rothova examined 361 uveitis patients who underwent a diagnostic paracentesis (FU patients were not included). No severe complications were encountered during follow-up (6 months to 3 years). A small hyphema was noticed in 5 out of 72 patients who were examined 30 minutes following the paracentesis. Despite the encouraging results, the authors only recommend the procedure to experienced ophthalmologists due to the potential risks of endophthalmitis, corneal abscess and cataract[107]. If the detection of rubella-specific intraocular antibodies is considered as an adequate diagnostic tool, it still needs to be determined when it is indicated to perform an anterior chamber tap. Intraocular antibody assay is costly and it may not be feasible to make it available for all patients with presumed FU. In patients with obvious heterochromia, cataract and vitreous opacities, who can be clinically diagnosed, it does not seem necessary to resort to a

paracentesis. In more subtle cases, Ab detection can be of value. The certainty of diagnosis of FU does not call for specific therapeutic measures, but it will prevent unnecessary and potentially harmful CS treatment.

6.6.4.8 CONCLUSION

Fuchs' uveitis should no longer be referred to as Fuchs' uveitis syndrome: the etiologic relationship with rubella virus has been convincingly documented in the last 5 years. How RV exposure ultimately leads to the clinical picture of FU is still a subject of debate. The lack of histologic evidence of viral particles in ocular tissue and the limited number of patients with detectable rubella genome make a persistent viral infection somewhat less likely. Laboratory testing can provide objective confirmation of the diagnosis and proves to be a valid test. The indications for diagnostic paracentesis are yet to be determined. Vaccination seems to prevent rather than cause FU. The detection of rubella genome in some FU patients raises a few questions. How long does this persistence last? Do patients with detectable rubella genome have a more severe disease course? A quantative analysis could provide additional information on the viral load. An investigation on the relationship with the severity of disease activity may also be interesting.

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Appendices

APPENDIX 1: LIST OF ABBREVIATIONS

ACAID: Anterior Chamber-Associated Immune Deviation

AH: Aqueous Humour

AI: Antibody Index

CS: Corticosteroids

CE: Cataract Extraction

CME: Cystoid Macular Edema

CMV: Cytomegalovirus

CRP: C-Reactive Protein

CRS: Congenital Rubella Syndrome

CTLA-4: Cytotoxic T-Lymphocyte Antigen 4

ECCE: Extracapsular Cataract Extraction

FU: Fuchs' Uveitis

GWC: Goldmann-Witmer Coefficient

HLA: Human Leukocyte Antigens

HSV: Herpes Simplex Virus

IAU: Idiopathic Anterior Uveitis

ICAM-1: Inter-Cellular Adhesion Molecule

ICCE: Intracapsular Cataract Extraction

ICGC: Idiopathic Chronic Granulomatous Iridocyclitis

ICI: Idiopathic Chronic Iridocyclitis

IOL: Intraocular Lens

IOP: Intraocular Pressure

IUSG: International Uveitis Study Group

IVCM: In Vivo Confocal Microscopy

KP: Keratic Precipitates

LR: Likelihood Ratio

MS: Multiple Sclerosis

OR: Odds Ratio

OS: Orthosympathetic/Orthosympathicus

PC IOL: Posterior Chamber Intraocular Lens

PE: Phacoemulsification

POAG: Primary Open-Angle Glaucoma

PPV: Pars Plana Vitrectomy

PSS: Posner-Schlossman Syndrome

RF: Rheumatoid Factor

RP: Retinitis Pigmentosa

RV: Rubella Virus

SSPE: Subacute Sclerosing Panencephalitis

UBM: Ultrasound Biomicroscopy

VA: Visual Acuity

VFD: Visual Field Defects

VZV: Varicella Zoster Virus

APPENDIX 2: 2-WAY CONTINGENCY TABLE ANALYSIS

Revised: 12/07/2010 -- Clarified definition of NNT: Number Needed to Treat (my thanks to Christopher Baethge for pointing this out)

This page computes various statistics from a 2-by-2 table. It will calculate the Yates-corrected chi-square, the Mantel-Haenszel chi-square, the Fisher Exact Test, and other indices relevant to various special kinds of 2-by-2 tables:

1. analysis of risk factors for unfavorable outcomes (odds ratio, relative risk, difference in proportions, absolute and relative reduction in risk, number needed to treat)
2. analysis of the effectiveness of a diagnostic criterion for some condition (sensitivity, specificity, pos & neg predictive values, pos & neg likelihood ratios, diagnostic and error odds ratios)
3. measures of inter-rater reliability (% correct or consistent, mis-classification rate, kappa, Forbes' NMI)
4. other measures of association (contingency coefficient, Cramer's phi coefficient, Yule's Q)

Many of these concepts are explained in detail in an online Evidence-based Medicine Glossary. For more information about a particular index, click on the <more info> link for that index.

Confidence intervals for the estimated parameters are computed by a general method (based on "constant chi-square boundaries") given in: *Statistical Methods for Rates and Proportions* (2nd Ed.) Section 5.6, by Joseph L. Fleiss (Pub: John Wiley & Sons, New York, 1981). This method is also described in Numerical Recipes in C (2nd Ed.) Section 15.6, by William H. Press et al. (Pub: Cambridge University Press, Cambridge UK, 1992)

Enter numbers into the four cells below. Make sure that the row and column totals add up correctly. Then click the Compute button.

Warning: Do not enter cell counts with a leading zero! That is, if a cell count is 34, enter it as 34, **not as 034**. Some browsers will mis-interpret some numbers entered with leading zeros, and will produce **wrong results** (with no warning message). For more information about this, and for other things to be aware of before using this page for the first time, make sure you read the JavaStat user interface guidelines.

Observed Contingency Table

*	Outcome Occurred	Outcome did not Occur	Totals
Risk Factor Present or Dx Test Positive	[ ] = a	[ ] = b	[ ] = r1
Risk Factor Absent or Dx Test Negative	[ ] = c	[ ] = d	[ ] = r2

Totals	= c1	= c2	= t

Confidence Level: 95 %

Chi-Square Tests

Type of Test	Chi Square	d.f.	p-value
Pearson Uncorrected		1	
Yates Corrected		1	
Mantel-Haenszel		1	

Fisher Exact Test

Type of comparison (Alternate Hypothesis)	p-value
Two-tailed (to test if the Odds Ratio is *significantly different* from 1): If you don't know which Fisher Exact p-value to use, **use this one**. This is the p-value produced by SAS, SPSS, R, and other software.	
Left-tailed (to test if the Odds Ratio is *significantly less* than 1):	
Right-tailed (to test if the Odds Ratio is *significantly greater* than 1):	
Two-tailed p-value calculated as described in Rosner's book: (2 times whichever is smallest: left-tail, right-tail, or 0.5) It tends to agree closely with Yates Chi-Square p-value.	
Probability of getting *exactly* the observed table: (This is not really a p-value; don't use this as a significance test.)	
Verification of computational accuracy: (This number should be very close to 1.0; the closer, the better.)	

Quantities derived from a 2-by-2 table

Quantities Derived from the 2-by-2 Contingency Table	Value		
Odds Ratio (OR) = (a/b)/(c/d);			

Relative Risk (RR) = (a/r1)/(c/r2);			
Kappa			
Overall Fraction Correct = (a+d)/t ; (often referred to simply as "Accuracy")			
Mis-classification Rate, = 1 - Overall Fraction Correct;			
Sensitivity = a/c1; (use exact Binomial confidence intervals instead of these)			
Specificity = d/c2; (use exact Binomial confidence intervals instead of these)			
Positive Predictive Value (PPV) = a/r1; (use exact Binomial confidence intervals instead of these)			
Negative Predictive Value (NPV) = d/r2; (use exact Binomial confidence intervals instead of these)			
Difference in Proportions (DP) = a/r1 - c/r2;			
Number Needed to Treat (NNT) = 1 / absolute value of DP; which = 1 / absolute value of ARR;			
Absolute Risk Reduction (ARR) = c/r2 - a/r1; which = - DP			
Relative Risk Reduction (RRR) = ARR/(c/r2); <more info>			
Positive Likelihood Ratio (+LR) = Sensitivity / (1 - Specificity);			
Negative Likelihood Ratio (-LR) = (1 - Sensitivity) / Specificity;			
Diagnostic Odds Ratio = (Sensitivity/(1-Sensitivity))/((1-Specificity)/Specificity);			
Error Odds Ratio = (Sensitivity/(1-Sensitivity))/(Specificity/(1-Specificity));			
Youden's J = Sensitivity + Specificity - 1;			

Number Needed to Diagnose (NND) = 1 / (Sensitivity - (1 - Specificity)) = 1 / (Youden's J); <more info>			
Forbes' NMI Index; <more info>			
Contingency Coefficient;			
Adjusted Contingency Coefficient;			
Phi Coefficient (= Cramer's Phi, and = Cohen's w Index, for 2x2 table);			
Yule's Q = (a*d-b*c)/(a*d+b*c) = (OR - 1) / (OR + 1); <more info>			
Equitable Threat Score = (a-e)/(a+b+c-e), where e = r1*c1/t; <more info>			
Entropy H(r) = - ((r1/t)$\log_2$(r1/t) + (r2/t)$\log_2$(r2/t))			
Entropy H(c) = - ((c1/t)$\log_2$(c1/t) + (c2/t)$\log_2$(c2/t))			
Entropy H(r,c) = - ((a/t)$\log_2$(a/t) + (b/t)$\log_2$(b/t) + (c/t)$\log_2$(c/t) + (d/t)$\log_2$(d/t))			
Information shared by descriptors r and c: B = H(r) + H(c) - H(r,c)			
A = H(r,c) - H(r)			
C = H(r,c) - H(c)			
Similarity of descriptors r and c: S(r,c) = B / (A + B + C)			
Distance between r and c: D(r,c) = (A + C) / (A + B + C)			

If you don't see your favorite "quantity" in this list,
drop me a line and let me know how that quantity is calculated from the four cell counts,
and I'll add it to the collection!

Reference: Bernard Rosner, *Fundamentals of Biostatistics*, 6th Ed., 2006

Return to the Interactive Statistics page or to the JCP Home Page

Send e-mail to John C. Pezzullo at jcp12345@gmail.com