

C-reactive Protein Level and Risk of Aging Macula Disorder

The Rotterdam Study

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Objective: To examine whether C-reactive protein (CRP) level is a risk factor for aging macula disorder (AMD) in a general population.

Methods: We examined serum high-sensitivity CRP (HsCRP) levels in 4914 participants of the population-based Rotterdam Study at risk for AMD. After a mean follow-up of 7.7 years, 561 cases of early and 97 cases of late incident AMD (iAMD) were identified. We used Cox proportional hazards regression models to estimate hazard ratios and corresponding 95% confidence intervals (CIs).

Results: After adjustment for age and sex, hazard ratios were 1.11 (95% CI, 1.02-1.21) per standard deviation

increase in HsCRP level for early iAMD and 1.28 (95% CI, 1.02-1.60) for late iAMD. Hazard ratios for early iAMD increased per quartile increase in HsCRP level as follows: second quartile, 1.19 (95% CI, 0.94-1.52); third quartile, 1.29 (95% CI, 1.01-1.64); and fourth quartile, 1.33 (95% CI, 1.05-1.70). The risk of late iAMD was higher in all upper quartiles of HsCRP.

Conclusion: Elevated baseline levels of HsCRP were associated with the development of early and late AMD in this large population-based cohort.

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SINCE THE FIRST DESCRIPTION of age-related macular degeneration in persons with senility,¹ at least 20 different names have been given to this disease according to views about its pathogenesis at various times. We now prefer the term *aging macula disorder* (AMD)² for the following reasons: *age-related* does not differentiate between juvenile macular disease and that associated with older age, it is open for debate if and when early or late AMD becomes a disease, and patients do not like disease names to be associated with senility or degeneration.

Aging macula disorder is a condition affecting the center of the retina in older persons. Late AMD is the main cause of incurable vision loss in the Western world,³⁻⁵ and its prevalence is estimated to double by 2020.⁶ Its pathogenesis is unclear, although some modifiable risk factors such as smoking and hypertension have been noted.⁷

Local inflammatory and immune-mediated events play a role in the development of drusen, the white subretinal extracellular deposits that are a hallmark of AMD.⁸⁻¹⁰ Direct analysis by liquid chro-

matography and immunocytochemical analyses confirmed that drusen contain proteins associated with inflammation such as fibrinogen, vitronectin, complement components, and C-reactive protein (CRP).^{11,12} Some of these proteins seem to be locally produced by damaged retinal pigment epithelium (RPE) cells.¹³ Also, inflammatory cells such as leukocytes and multinucleated giant cells have been described in the choroid of eyes with late AMD and in excised choroidal neovascular membranes.¹⁴⁻¹⁷

Chronic inflammation seems to be a causative factor in the development of AMD. Studies have investigated this possible association from different perspectives. A mouse model with defects in macrophage mobilization demonstrated many pathologic features of AMD, suggesting that macrophage dysfunction plays a role in AMD.¹⁸ Data from a case-control study¹⁹ demonstrated an association between antibodies against *Chlamydia pneumoniae* and wet (neovascular) late AMD. In addition, a modest association was found between pigmentary abnormalities and wet late AMD and emphysema, and gout was associated with dry late AMD.²⁰ Recently, a

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strong association between the Y402H single-nucleotide polymorphism in the complement factor H (CFH) gene and AMD was found in 3 clinic-based case-control studies²¹⁻²³ and in a longitudinal population-based study.²⁴ Complement factor H has an essential role in the inhibition of the alternative complement pathway, and abnormal regulation of this pathway leads to an increased inflammatory state.

C-reaction protein is a nonspecific marker of systemic inflammation. It activates the classic route of complement activation directly and via cytokines through Fc receptor-binding by antibodies, which enhances the inflammatory response.¹² Two clinic-based cross-sectional studies^{25,26} and a longitudinal clinical study²⁷ reported an association between CRP level and AMD, supporting the inflammatory pathogenesis of AMD. We investigated whether baseline serum high-sensitivity CRP (HsCRP) serum levels were a risk factor for AMD in the general population.

METHODS

POPULATION

The Rotterdam Study is a prospective population-based cohort study investigating the incidence and determinants of chronic disabling diseases in older persons. All inhabitants 55 years or older living in a suburb of Rotterdam, the Netherlands, were invited to enroll.²⁸ Of 10 275 eligible individuals, 7983 (77.7%) participated. The ophthalmologic part of the study started after screening of the participants had begun, leading to 6780 ophthalmic participants (response rate, 78%). The tenets of the Declaration of Helsinki were followed, and the appropriate medical ethics committees approved the study. All participants signed an informed consent form and gave permission to retrieve information from medical records. Baseline examinations included a home interview and physical examinations at the research center, were conducted from 1990 until 1993, and were followed by 3 examinations from 1993 to 1994 (response rate, 88%), from 1997 to 1999 (response rate, 80%), and from 2000 to 2004 (response rate, 74%).

MEASUREMENT OF HsCRP

At baseline, a nonfasting blood sample was collected and processed using standard techniques and was stored at -20°C .²⁹ In 2003 and 2004, serum levels of HsCRP were determined using the rate near-infrared particle immunoassay method (IMMAGE high-sensitive CRP, Beckman Coulter, Fullerton, California). This system measures concentrations ranging from 0.2 to 1140 mg/L (to convert to nanomoles per liter, multiply by 9.524), with a within-run precision of less than 5.0%, a total precision of less than 7.5%, and a reliability coefficient of 0.995. In a random sample of the study ($n=29$), we compared HsCRP measurements in baseline blood samples from the same participants stored at -20°C and -80°C . The correlation between these measurements was high (Spearman rank correlation, 0.99; $P<.001$), although HsCRP levels were somewhat lower in blood stored at -20°C (mean difference, -0.5097 ; 95% confidence interval [CI], -1.637 to 0.618). This difference was not statistically significant. Because we used these -20°C stored samples for all our analyses, we do not expect that this affected our point estimates. The HsCRP distribution was skewed. Outliers (with values >3 SDs of the population distribution) of the logarithmically transformed HsCRP values were excluded from the

analyses because of the possible presence of an acute inflammatory disease.²⁹

AMD DEFINITION

For the diagnosis of AMD, 35° color pictures were taken of the macular area of each eye (TRV-50VT fundus camera; Topcon Corporation, Tokyo, Japan) after dilatation of the pupils using a combination of 0.5% tropicamide and 5% phenylephrine hydrochloride. These transparencies and digitized images at the last follow-up visit were graded using $\times 12.5$ magnification according to an international classification and grading system³⁰ by the same 2 trained professionals grading AMD from baseline onward, who were masked for all other determinants.^{31,32} We deviated from this system by discontinuing use of the term *age-related maculopathy* in AMD and by categorizing the range of AMD fundus signs into 5 mutually exclusive stages of 0 through 4 that represent increasing risk of late AMD.³² Stage 0 denoted no signs of AMD or hard drusen only ($<63\ \mu\text{m}$); stage 1 denoted soft distinct drusen ($\geq 63\ \mu\text{m}$) or pigmentary abnormalities. Because we wanted to have for our analyses a clear delineation between participants with no AMD and early AMD and because some participants with only 1 or 2 soft distinct drusen were classified as having stage 1 AMD, we considered stage 1 as no AMD in the present analyses. We included soft indistinct drusen ($\geq 125\ \mu\text{m}$) or reticular drusen only or soft distinct drusen ($\geq 63\ \mu\text{m}$) with pigmentary abnormalities as stage 2 early AMD, and we included soft indistinct drusen ($\geq 125\ \mu\text{m}$) or reticular drusen with pigmentary abnormalities as stage 3 early AMD. Stage 4 denoted late AMD and was usually associated with severe visual loss.³² Late AMD was subdivided into dry (geographic atrophy) and wet (neovascular) AMD. A person was classified according to the highest stage of AMD in either eye and was considered as having wet AMD if both dry and wet AMD were present. Early incident AMD (iAMD) was defined as any sign of early AMD in at least 1 eye during follow-up among participants with no AMD at baseline in either eye. Persons who were free of late AMD at baseline in both eyes and developed it in at least 1 eye during follow-up were classified as having late iAMD.

POPULATION FOR ANALYSIS

At baseline, gradable fundus transparencies of 6418 participants were available, of whom 476 (7.4%) had early AMD and 106 (1.7%) had late AMD. This resulted in 5836 persons being at risk for early or late AMD and 6312 persons being at risk for late AMD only. Of 6312 participants at risk for early and late iAMD, 4914 (77.9% of those at risk) participated in at least 1 follow-up examination. Our study population consisted of 4624 participants (73.3%) from these subjects in whom we had baseline HsCRP measurements. Serum HsCRP levels were missing from persons who did not visit the research center or who refused blood sampling and from persons in whom no blood sample was available because of various logistic reasons. We excluded 20 persons (0.43%) at risk of any AMD who had outlying HsCRP levels, leaving 4604 participants as our population for analysis.

ASSESSMENT OF CONFOUNDERS

Information on all potential confounders was collected at baseline. During a home interview, trained research assistants asked participants about their smoking habits. Smoking was categorized as current, past, or never smoker. Anthropometric measurements were obtained at the research center. Body mass index was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressures were mea-

Table 1. Baseline Characteristics of 4604 Participants^a

Variable	No AMD (n=3946)	Early Incident AMD (n=561)	Late Incident AMD (n=97)
Age, y	66.7±7.7	68.2±7.6	72.0±6.5
Female sex	2315 (58.7)	315 (56.1)	55 (56.7)
Smoking status ^b			
Never	1324 (33.8)	186 (33.6)	26 (27.7)
Past	1705 (43.6)	240 (43.4)	43 (45.7)
Current	886 (22.6)	127 (23.0)	25 (26.6)
Diabetes mellitus	362 (9.2)	39 (7.0)	8 (8.2)
Body mass index ^c	26.4±3.7	26.2±3.5	26.1±3.3
Blood pressure, mm Hg			
Systolic	137.5±21.7	138.9±20.7	139.1±19.5
Diastolic	74.0±11.1	73.4±11.2	71.8±11.1
Cholesterol level, mg/dL			
Total	259±46	255±46	255±42
High-density lipoprotein	50±15	54±15	50±15

Abbreviation: AMD, aging macular disorder.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

^aData are given as mean±SD or as number (percentage).

^bBecause of missing data, numbers do not sum to heading totals and percentages are not based on heading totals.

^cCalculated as weight in kilograms divided by height in meters squared.

sured twice at the right brachial artery using a random zero sphygmomanometer when the participant was in a sitting position. The mean of these 2 measurements was used to determine blood pressure levels. Nonfasting blood samples were obtained from all participants. Serum total cholesterol and high-density lipoprotein cholesterol levels were measured using an automated enzymatic procedure. Diabetes mellitus was considered to be present when persons used blood glucose-lowering medication or had a nonfasting or postload glucose level above 198 mg/dL (to convert to millimoles per liter, multiply by 0.0555).

DATA ANALYSIS

We investigated associations between HsCRP levels and early or late iAMD using Cox proportional hazards regression models to compute hazard ratios (HRs) and corresponding 95% CIs. Follow-up time in years was used as the time axis of the model. Time to event is included when calculating HRs and HRs can be interpreted as relative risks. Linear trends were analyzed in which the regression coefficient was expressed per standard deviation increase, and quartiles were analyzed continuously and as categorical variables. All analyses were initially adjusted for age and sex. To check whether associations could be attributed to confounding, analyses were repeated with possible confounders added to the model (history of smoking or diabetes mellitus, body mass index, diastolic and systolic blood pressures, and total and high-density lipoprotein cholesterol levels). All analyses were performed using commercially available software (SPSS version 11.0; SPSS Inc, Chicago, Illinois).

RESULTS

Baseline characteristics of participants free of any AMD at the time and of those with early or late iAMD are given in **Table 1**. Persons with missing HsCRP values were on average older, were more likely to be female, more frequently resided in a nursing home, and had lower high-

Table 2. Risk of Early Incident Aging Macula Disorder for Quartiles of Baseline High-Sensitivity C-reactive Protein Level

Quartile (Range)	No. (Cases)	HR (95% CI) ^a	HR (95% CI) ^b
1 (≤0.83)	1135 (123)	1 [Reference]	1 [Reference]
2 (0.84-1.72)	1132 (146)	1.19 (0.94-1.52)	1.26 (0.99-1.61)
3 (1.73-3.25)	1116 (147)	1.29 (1.01-1.64)	1.35 (1.05-1.74)
4 (≥3.26)	1124 (145)	1.33 (1.05-1.70)	1.40 (1.08-1.81)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age and sex. *P*=.02 for trend.

^bAdditionally adjusted for smoking, body mass index, diabetes mellitus, systolic and diastolic blood pressures, and total cholesterol and high-density cholesterol levels. *P*=.01 for trend.

Table 3. Risk of Late Incident Aging Macula Disorder for Quartiles of Baseline High-Sensitivity C-reactive Protein Level

Quartile (Range)	No. (Cases)	HR (95% CI) ^a	HR (95% CI) ^b
1 (≤0.83)	1028 (16)	1 [Reference]	1 [Reference]
2 (0.84-1.72)	1010 (24)	1.34 (0.71-2.54)	1.35 (0.70-2.58)
3 (1.73-3.22)	999 (30)	1.90 (1.03-3.49)	1.96 (1.04-3.69)
4 (≥3.23)	1006 (27)	1.95 (1.05-3.63)	1.79 (0.92-3.48)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age and sex. *P*=.02 for trend.

^bAdditionally adjusted for smoking, body mass index, diabetes mellitus, systolic and diastolic blood pressures, and total cholesterol and high-density cholesterol levels. *P*=.05 for trend.

density lipoprotein cholesterol levels. Follow-up of participants was, on average, 7.7 years (median follow-up, 10.4 years [follow-up range, 0.3-13.9 years]). During this period, 658 persons were diagnosed as having any iAMD, 561 of whom developed early iAMD and 97 of whom developed late iAMD. Among all participants with iAMD, HsCRP levels ranged from 0.20 to 33.60 mg/L (mean±SD, 2.67±3.22 mg/L); HsCRP levels ranged from 0.20 to 31.50 mg/L (mean±SD, 2.69±3.08 mg/L) in those with early iAMD and from 0.20 to 16.80 mg/L (mean±SD, 3.04±3.18 mg/L) in those with late iAMD.

The risk of early iAMD rose per standard deviation increase in HsCRP level after adjustment for age and sex (HR, 1.11; 95% CI, 1.02-1.21) and after multivariate adjustment (HR, 1.11; 95% CI, 1.02-1.22). As **Table 2** summarizes, the risk of early iAMD also increased with each higher quartile of HsCRP. Additional adjustment for cardiovascular covariates did not substantially change this.

The risk of late iAMD rose per standard deviation increase in HsCRP level (HR, 1.31; 95% CI, 1.06-1.61) and after additional adjustments (HR, 1.28; 95% CI, 1.02-1.60). As **Table 3** summarizes, the risk of late iAMD was higher in all upper quartiles of HsCRP. However, this only reached statistical significance in the third quartile of the fully adjusted model. The results adjusted for age and sex follow a dose-response pattern, but this effect was lost after additional adjustments, probably because of a more limited sample size for late AMD.

In this population-based cohort, we confirmed data from 3 clinic-based studies²⁵⁻²⁷ indicating that baseline HsCRP levels were associated with early and late iAMD, with the highest risks in late iAMD. This supports the theory that inflammation is a mechanism involved in the pathogenesis of AMD in the general population.²⁴

Injury to the RPE and possibly to the choroid caused by smoking, obesity, the toxic effect of light, and low antioxidant intake may induce AMD through a state of chronic inflammation.^{2,25} Choroidal dendritic cells, which are associated with drusen, respond to locally damaged RPE cells and migrate to the site of tissue damage.¹⁰ Dendritic cells trigger immune-mediated pathways. In persons with AMD, the down-regulation of the immune response may be hampered, resulting in a state of chronic inflammation of the RPE and damage to the underlying Bruch membrane, leading to progression of AMD.¹⁰

Evidence is accumulating that inflammatory and immune-associated pathways have a role in other degenerative diseases associated with advancing age such as atherosclerosis and Alzheimer disease.³³⁻³⁶ Drusen components have been found in atherosclerotic plaques and deposits in Alzheimer disease,¹² and AMD, atherosclerosis, and Alzheimer disease may partly share a similar inflammatory pathogenesis.

Differential misclassification is unlikely in our study because AMD graders were masked for HsCRP status and because HsCRP data were collected without knowledge of AMD status. Persons who refused to participate or were lost to follow-up were older and less healthy.³² If persons with higher HsCRP levels and AMD would selectively not have participated, selection bias would have been introduced. We think this is unlikely because subjects were unaware of their HsCRP level and would be aware of symptoms only in late iAMD. We measured HsCRP levels only once. This should not be problematic because HsCRP has a long half-life of approximately 19 hours³⁷ and because concentrations seem to be fairly stable for at least 5 years in most individuals.^{38,39} Furthermore, there is no circadian variation and no evidence for seasonal variations in HsCRP levels.^{38,40-42}

Large-scale prospective studies^{43,44} demonstrated that elevated levels of HsCRP are an independent predictor of future cardiovascular events in healthy individuals. In addition to predicting cardiovascular death and myocardial infarction, serum HsCRP level is a predictor of stroke and the development of peripheral arterial disease.⁴⁵ Although not yet proven, it is hypothesized that CRP directly promotes atherosclerosis and functions as a mediator in the process.⁴⁵⁻⁴⁹ C-reactive protein level-lowering treatments (eg, the use of statins or improvement of lifestyles) are associated with reduced cardiovascular risks.^{39,45,50,51}

Atherosclerosis is a known risk factor for AMD, most likely through decreased choroidal blood flow, directly or indirectly impairing the functioning of the RPE.^{52,53} Atherosclerosis is associated with elevated HsCRP levels, which could explain the higher risk of AMD.³⁶ After correction for cardiovascular risk factors, the linear trend analysis for early iAMD remained statistically signifi-

cant, but this was statistically nonsignificant for late iAMD. Statistical power due to the lower number of late iAMD cases could have caused the loss of significance, especially because the HR was still elevated.

Complement factor H is an essential regulator in the complement system. It inactivates C3b and functions as an activation inhibitor of the alternative complement pathway.^{54,55} Because of the *CFH* Y402H single-nucleotide polymorphism,²¹⁻²⁴ complement activation is less suppressed, leading to an increased inflammatory reaction. This single-nucleotide polymorphism is located in a region that contains the binding sites for heparin and CRP. Complement factor H binds to CRP, which may help inhibit the CRP-dependent alternative pathway activation induced by damaged tissue.⁵⁴ Complement factor H tends to prevent the assembly of complement complex in the arterial intima.⁵⁶ It has been suggested that allele-specific changes in activities of the binding sites for heparin and CRP modify the protective action of complement factor H.²² Complement-related damage to choroidal vessels might lead to wet AMD.^{22,23}

It is possible that reduction of CRP levels might lower the risk of AMD. A substance that can selectively inhibit CRP synthesis has not yet been developed, to our knowledge. Smoking and high body mass index increase CRP levels. Moderate alcohol intake, diets with a low glycemic index, and statin and multivitamin use reduce CRP levels.^{46,57} Additional correction for smoking and obesity, also associated with a higher risk of AMD, did not change our point estimates. Nevertheless, reducing both might have a protective effect.

As mentioned, 2 clinical cross-sectional studies^{25,26} and a longitudinal study²⁷ found an association between CRP level and AMD, while a population-based longitudinal study⁵⁸ and a population-based cross-sectional study⁵⁹ did not confirm this. However, the latter 2 studies included fewer cases, especially cases with late AMD. It has been suggested that differences in results could be attributed to the possibility that inflammation may have a larger role in the pathogenesis of progression to late AMD compared with that of early AMD.⁵⁸ However, in the present study, we found an association of HsCRP level not only with late iAMD but also with early iAMD. This is in line with the known progression over the years from stage 0 to stage 4 AMD and supports the inflammatory pathogenesis of early and late AMD. Finally, clinic-based and cross-sectional studies are more prone to selection bias; therefore, we believe that confirmation by a longitudinal population-based study is important.

In conclusion, persons with a high HsCRP level (>1.73 mg/L) within the normal range have a statistically significant higher risk of early and late AMD. We consider HsCRP level a potential useful biological marker in profiling the risk of AMD for individual persons.

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REFERENCES

- Hutchinson J. Symmetrical central choroido-retinal disease occurring in senile persons. *R London Ophthalmic Hosp Rep J Ophthalmic Med Surg.* 1874;(8):231-244.
- de Jong PT. Age-related macular degeneration. *N Engl J Med.* 2006;355(14):1474-1485.
- Attebo K, Mitchell P, Smith W. Visual acuity and the causes of visual loss in Australia: the Blue Mountains Eye Study. *Ophthalmology.* 1996;103(3):357-364.
- Klaver CC, Wolfs RC, Vingerling JR, Hofman A, de Jong PT. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Arch Ophthalmol.* 1998;116(5):653-658.
- Tielsch JM, Javitt JC, Coleman A, Katz J, Sommer A. The prevalence of blindness and visual impairment among nursing home residents in Baltimore. *N Engl J Med.* 1995;332(18):1205-1209.
- Friedman DS, O'Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol.* 2004;122(4):564-572.
- van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong PT. Epidemiology of age-related maculopathy: a review. *Eur J Epidemiol.* 2003;18(9):845-854.
- Penfold PL, Madigan MC, Gillies MC, Provis JM. Immunological and aetiological aspects of macular degeneration. *Prog Retin Eye Res.* 2001;20(3):385-414.
- Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in drusen formation and age related macular degeneration. *Exp Eye Res.* 2001;73(6):887-896.
- Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res.* 2001;20(6):705-732.
- Crabb JW, Miyagi M, Gu X, et al. Drusen proteome analysis: an approach to the etiology of age-related macular degeneration [published online ahead of print October 21, 2002]. *Proc Natl Acad Sci U S A.* 2002;99(23):14682-14687. doi:10.1073/pnas.222551899.
- Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol.* 2002;134(3):411-431.
- Roth F, Bindewald A, Holz FG. Key pathophysiologic pathways in age-related macular disease [published online ahead of print August 10, 2004]. *Graefes Arch Clin Exp Ophthalmol.* 2004;242(8):710-716.
- Penfold PL, Killingsworth MC, Sarks SH. Senile macular degeneration: the involvement of immunocompetent cells. *Graefes Arch Clin Exp Ophthalmol.* 1985;223(2):69-76.
- Killingsworth MC, Sarks JP, Sarks SH. Macrophages related to Bruch's membrane in age-related macular degeneration. *Eye.* 1990;4(pt 4):613-621.
- Seregard S, Algere PV, Berglin L. Immunohistochemical characterization of surgically removed subfoveal fibrovascular membranes. *Graefes Arch Clin Exp Ophthalmol.* 1994;232(6):325-329.
- Hutchinson AK, Grossniklaus HE, Capone A. Giant-cell reaction in surgically excised subretinal neovascular membrane. *Arch Ophthalmol.* 1993;111(6):734-735.
- Ambati J, Anand A, Fernandez S, et al. An animal model of age-related macular degeneration in senescent Ccl-2- or Ccr-2-deficient mice [published online ahead of print October 19, 2003]. *Nat Med.* 2003;9(11):1390-1397. doi:10.1038/nm950.
- Kalayoglu MV, Galvan C, Mahdi OS, Byrne GI, Mansour S. Serological association between *Chlamydia pneumoniae* infection and age-related macular degeneration. *Arch Ophthalmol.* 2003;121(4):478-482.
- Klein R, Klein BE, Tomany SC, Cruickshanks KJ. Association of emphysema, gout, and inflammatory markers with long-term incidence of age-related maculopathy. *Arch Ophthalmol.* 2003;121(5):674-678.
- Edwards AO, Ritter R III, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration [published online ahead of print March 10, 2005]. *Science.* 2005;308(5720):421-424. doi:10.1126/science.1110189.
- Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration [published online ahead of print March 10, 2005]. *Science.* 2005;308(5720):419-421. doi:10.1126/science.1110359.
- Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration [published online ahead of print March 10, 2005]. *Science.* 2005;308(5720):385-389. doi:10.1126/science.1109557.
- Despriet DD, Klaver CC, Wittman JC, et al. Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. *JAMA.* 2006;296(3):301-309.
- Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration. *JAMA.* 2004;291(6):704-710.
- Vine AK, Stader J, Branham K, Musch DC, Swaroop A. Biomarkers of cardiovascular disease as risk factors for age-related macular degeneration [published online ahead of print October 12, 2005]. *Ophthalmology.* 2005;112(12):2076-2080. doi:10.1016/j.ophtha.2005.07.004.
- Seddon JM, George S, Rosner B, Rifai N. Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. *Arch Ophthalmol.* 2005;123(6):774-782.
- Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol.* 1991;7(4):403-422.
- Van der Meer IM, De Maat MP, Hak AE, et al. C-reactive protein predicts progression of atherosclerosis measured at various sites in the arterial tree: the Rotterdam Study. *Stroke.* 2002;33(12):2750-2755.
- Bird AC, Bressler NM, Bressler SB, et al; International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol.* 1995;39(5):367-374.
- van Leeuwen R, Chakravarthy U, Vingerling JR, et al. Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film? *Ophthalmology.* 2003;110(8):1540-1544.
- van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong PT. The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study [published correction appears in *Arch Ophthalmol.* 2003;121(7):955]. *Arch Ophthalmol.* 2003;121(4):519-526.
- Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging.* 2000;21(3):383-421.
- Glass CK, Witztum JL. Atherosclerosis: the road ahead. *Cell.* 2001;104(4):503-516.
- Ross R. Atherosclerosis is an inflammatory disease. *Am Heart J.* 1999;138(5, pt 2):S419-S420.
- van der Meer IM, de Maat MP, Bots ML, et al. Inflammatory mediators and cell adhesion molecules as indicators of severity of atherosclerosis: the Rotterdam Study. *Arterioscler Thromb Vasc Biol.* 2002;22(5):838-842.
- Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radiiodinated human C-reactive protein in health and disease. *J Clin Invest.* 1993;91(4):1351-1357.
- Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin Chem.* 1997;43(1):52-58.
- Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E; Cholesterol and Recurrent Events (CARE) Investigators. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation.* 1999;100(3):230-235.
- Fröhlich M, Sund M, Russ S, et al. Seasonal variations of rheological and hemostatic parameters and acute-phase reactants in young, healthy subjects. *Arterioscler Thromb Vasc Biol.* 1997;17(11):2692-2697.
- Fröhlich M, Sund M, Thorand B, Hutchinson WL, Pepys MB, Koenig W. Lack of seasonal variation in C-reactive protein. *Clin Chem.* 2002;48(3):575-577.
- Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. *Clin Chem.* 2001;47(3):426-430.
- Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary

- heart disease: prospective study and updated meta-analyses. *BMJ*. 2000;321(7255):199-204.
44. van der Meer IM, de Maat MP, Kiliaan AJ, van der Kuip DA, Hofman A, Witteman JC. The value of C-reactive protein in cardiovascular risk prediction: the Rotterdam Study. *Arch Intern Med*. 2003;163(11):1323-1328.
 45. Koenig W. Predicting risk and treatment benefit in atherosclerosis: the role of C-reactive protein. *Int J Cardiol*. 2005;98(2):199-206.
 46. Labarrere CA, Zaloga GP. C-reactive protein: from innocent bystander to pivotal mediator of atherosclerosis. *Am J Med*. 2004;117(7):499-507.
 47. Hackam DG, Anand SS. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. *JAMA*. 2003;290(7):932-940.
 48. Chait A, Han CY, Oram JF, Heinecke JW. Thematic review series: the immune system and atherogenesis: lipoprotein-associated inflammatory proteins: markers or mediators of cardiovascular disease [published online ahead of print February 1, 2005]? *J Lipid Res*. 2005;46(3):389-403. doi:10.1194/jlr.R400017-JLR200.
 49. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 2005;352(1):29-38.
 50. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286(1):64-70.
 51. Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins [published online ahead of print March 24, 2005]. *Arterioscler Thromb Vasc Biol*. 2005;25(6):1231-1236. doi:10.1161/01.ATV.0000163840.63685.0.
 52. van Leeuwen R, Ikram MK, Vingerling JR, Witteman JC, Hofman A, de Jong PT. Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2003;44(9):3771-3777.
 53. Friedman E. The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration. *Am J Ophthalmol*. 2000;130(5):658-663.
 54. Rodríguez de Córdoba S, Esparza-Gordillo J, Goicoechea de Jorge E, Lopez-Trascasa M, Sanchez-Corral P. The human complement factor H: functional roles, genetic variations and disease associations. *Mol Immunol*. 2004;41(4):355-367.
 55. Zipfel PF, Skerka C, Hellwege J, et al. Factor H family proteins: on complement, microbes and human diseases. *Biochem Soc Trans*. 2002;30(pt 6):971-978.
 56. Oksjoki R, Jarva H, Kovanen PT, Laine P, Meri S, Pentikainen MO. Association between complement factor H and proteoglycans in early human coronary atherosclerotic lesions: implications for local regulation of complement activation [published online ahead of print January 23, 2003]. *Arterioscler Thromb Vasc Biol*. 2003;23(4):630-636. doi:10.1161/01.ATV.0000057808.91263.A4.
 57. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107(3):499-511.
 58. Klein R, Klein BE, Knudtson MD, Wong TY, Shankar A, Tsai MY. Systemic markers of inflammation, endothelial dysfunction, and age-related maculopathy. *Am J Ophthalmol*. 2005;140(1):35-44.
 59. McGwin G, Hall TA, Xie A, Owsley C. The relation between C reactive protein and age related macular degeneration in the Cardiovascular Health Study. *Br J Ophthalmol*. 2005;89(9):1166-1170.

From the Archives of the Archives

Among the conditions favorably influenced by electricity were:

- a. Trigeminal neuralgia, especially supraorbital. In symptomatic neuralgia, as that complicating a brain tumor or from rheumatism, the treatment is of no avail, but in pure neuralgia, Silex claims that there is no treatment superior to electricity. The anode is placed on the tender point, and the cathode on the neck (Sperling).
- b. Fibrillary twitching of the lids which have resisted other methods disappear in a few sittings.
- c. Scleritis and episcleritis; in cases where skilful treatment has brought slight or passing improvement, and where one relapse after another incapacitates the patient for years, when the disease is not syphilitic, electricity is of great service.

Reference: Silex. Clinical and experimental observations in electrotherapy in ocular diseases. *Arch Ophthalmol*. 1902;31:565.