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Studies of Male Survivors of Myocardial Infarction due to  
"Essential" Atherosclerosis

III. Corneal Arcus:  
Incidence and Relation to Serum Lipids and Lipoproteins

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ABSTRACT

Corneal arcus and serum lipids were studied in 121 men, aged 30 to 80, with atherosclerotic coronary heart disease (CHD), and in healthy controls. In both groups the incidence of arcus increased from 55% in the fifth decade to 90% in the eighth. Under 40, arcus was a significant differentiating sign, being present in 11 of the 25 coronary patients and in none of the controls. In both groups, to age 60, the incidence of arcus correlated with serum cholesterol and phospholipid but not with standard Sf 0-400 lipoprotein fractions. In the CHD group there was significant elevation of the serum lipids. Since arcus is itself a fatty infiltration of the eye, these findings support the importance of serum lipids in atherogenesis. Clinically, corneal arcus in a male under 40 may be a clue to hyperlipidemia and a propensity to CHD.

SOMMAIRE

On a étudié la présence de gérontoxon et la lipémie chez 121 hommes, âgés de 30 à 80 ans, atteints de maladie coronaire (MC) d'origine athérosclérotique et chez des sujets sains servant de témoins. Dans les deux groupes, la fréquence du gérontoxon a augmenté de 55% à partir de la cinquième décennie jusqu'à 90% dans la huitième. En dessous de 40 ans, la présence de gérontoxon constituait un signe différentiel certain, étant donné qu'elle existait chez 11 des 25 coronariens et était inexistante chez les sujets témoins. Dans les deux groupes, jusqu'à 60 ans, la fréquence du gérontoxon correspondait au niveau du cholestérol et des phospholipides sanguins, mais n'avait pas de relation avec la concentration classique des fractions lipoprotidiques Sf 0-400. Dans les groupes des malades souffrant de MC, la lipémie était notablement plus élevée. Etant donné que l'arc cornéen sénile est, en soi même, une infiltration lipidique de l'oeil, ces constatations confirment l'importance de la lipémie comme facteur étiologique de l'athérosclérose. En clinique, l'arc sénile cornéen chez un homme de moins de 40 ans est une indication de possibilité d'hyperlipémie et de propension à la MC.

A CONNECTION between corneal arcus (arcus senilis) and arteriosclerosis has been suspected for at least a century, but statistics for and against their clinical association are still being reported.<sup>1</sup> The relation of corneal arcus to the level of serum cholesterol has also remained controversial.<sup>2</sup> Consequently, the incidence of arcus and its relation to serum lipids were examined in the course of studies of coronary heart disease (CHD) due to "essential" atherosclerosis, i.e. atherosclerosis not accompanied by any complicating conditions.

CLINICAL MATERIAL AND METHODS

The selection and investigation of the coronary and control subjects have been described in detail previously.<sup>3-5</sup> In brief, the coronary patients were survivors of myocardial infarction. Valvular disease, syphilis, anemia or polycythemia, throm-

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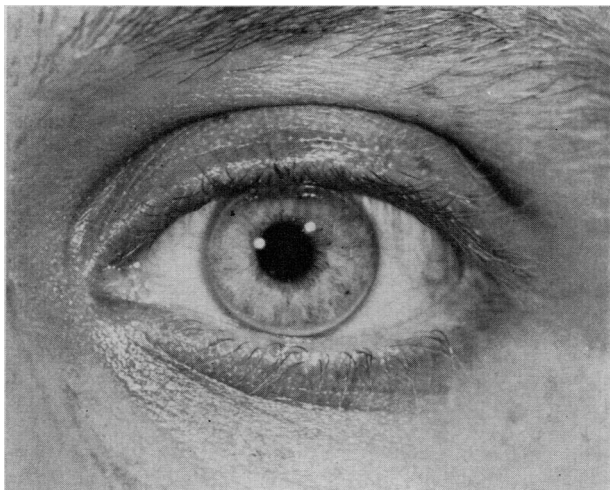


Fig. 1.—Well-developed corneal arcus in a young hypercholesterolemic coronary patient. Note the clear zone separating the opacity from the limbus.

boangiitis obliterans or polyarteritis nodosa having been excluded, the cause for the ischemic heart disease was, in every instance, almost certainly atherosclerosis. All were free of hypertension (persistent elevation of the blood pressure above 150/90 mm. Hg), diabetes, nephrosis and hypothyroidism, or any major disease. The control group consisted of healthy men, matched by age.

The participants were examined for the macroscopic presence of corneal arcus. Each eye was meticulously inspected in full daylight with the help of a small beam of artificial light directed at the limbus area from various angles. It is important to realize that under less favourable lighting conditions slight degrees of the lesion are easily missed, and that experience facilitated the more frequent recognition of these lesions.<sup>8</sup> Care was taken to be certain that the opacity was separated from the limbus by a clear zone (Fig. 1). This latter differentiates arcus from embryotoxon, an angular lipid-free opacity of the cornea, which is continuous with the sclera at the limbus.<sup>7</sup>

#### COMPOSITION OF THE GROUPS

All of the subjects in the study were males. The numbers and ages are shown in Table I. Up to age 70, there were approximately 25 patients in each decade, and their mean ages were similar.

A general characterization of the subjects was presented in an earlier report.<sup>3</sup> In both groups the total fat consumption was 38% of ingested calories, but the control group tended to eat more calories and more milk fat.<sup>8</sup> The coronary group (Canadian, male, military veterans, survivors of previous myocardial infarction, with no aggravating and no associated disease) certainly would not be representative of the coronary population as a whole. However, this design permits a study of the relationship between serum lipids, CHD and corneal arcus with a minimum of other variables.

TABLE I.—COMPOSITION OF THE GROUPS: NUMBER AND AGE

Decade	Control			Coronary		
	n	Mean age	s	n	Mean age	s
4th	25	34.4	2.9	25	36.3	2.8
5th	25	43.6	2.7	26	44.5	3.0
6th	27	56.0	2.4	28	55.5	2.4
7th	23	64.1	2.8	23	64.3	2.7
8th	21	73.0	2.9	12	73.8	3.1
	121			114		

n = number; s = standard deviation.

## RESULTS

### CORNEAL ARCUS

#### Prevalence

The prevalence of corneal arcus is shown in Table II. The striking finding is the earlier appearance of arcus in the coronary group. In the fourth decade it was present in 11 out of 25 coronary patients but absent in all 25 controls. This difference is highly significant ( $p < 0.001$ ). In all of the later decades, the incidence was similar in both groups, about 55% in the fifth to 90% in the eighth decade.

TABLE II.—CORNEAL ARCUS: PREVALENCE

Decade	Control	Coronary
4th.....	0/25	11/25
5th.....	12/25	15/26
6th.....	17/27	13/28
7th.....	18/23	18/23
8th.....	19/21	11/12

The upper figure is the number of subjects with corneal arcus; the lower, the total number.

#### Degree

Where corneal arcus was present, its degree was arbitrarily classified as slight, moderate or marked. The severity of arcus often differed slightly in the two eyes, but never by more than one degree. The patient was classified according to the status of the worse eye. Table III shows that in both groups there is a tendency for an increase in degree of arcus with age.

TABLE III.—CORNEAL ARCUS: DEGREE

Decade	Control			Coronary		
	Slight	Moderate	Marked	Slight	Moderate	Marked
4th	0	0	0	10	0	1
5th	7	4	1	9	3	3
6th	10	6	1	9	2	2
7th	4	9	5	7	6	5
8th	5	5	9	4	5	2

### RELATION OF INCIDENCE OF ARCUS TO SERUM LIPIDS

#### Total Cholesterol

Table IV relates the presence of corneal arcus to the levels of total serum cholesterol. In the fourth to sixth decades of both groups, the subjects

TABLE IV.—CORNEAL ARCUS: RELATION TO SERUM TOTAL CHOLESTEROL\*

Decade	Control		Coronary	
	No arcus	With arcus	No arcus	With arcus
4th	204.9 ± 28.7	None	269.9 ± 41.5	209.4 ± 65.0
5th	208.4 ± 42.9	222.0 ± 32.5	251.9 ± 23.6	269.7 ± 36.4
6th	196.6 ± 30.0	212.4 ± 33.6	229.7 ± 37.5	273.5 ± 46.4
7th	241.4 ± 47.3	208.7 ± 31.3	223.6 ± 35.4	233.4 ± 36.8
8th	246.5 ± 77.1	208.9 ± 34.0	330.0	225.0 ± 42.3

\*Mg.%, mean and standard deviation.  
See Table II for the numbers of subjects, and Table V for the probability levels.

with arcus tended to have higher mean cholesterol levels than those without arcus. This is illustrated in Fig. 2. Table V shows the probability levels for

TOTAL SERUM CHOLESTEROL

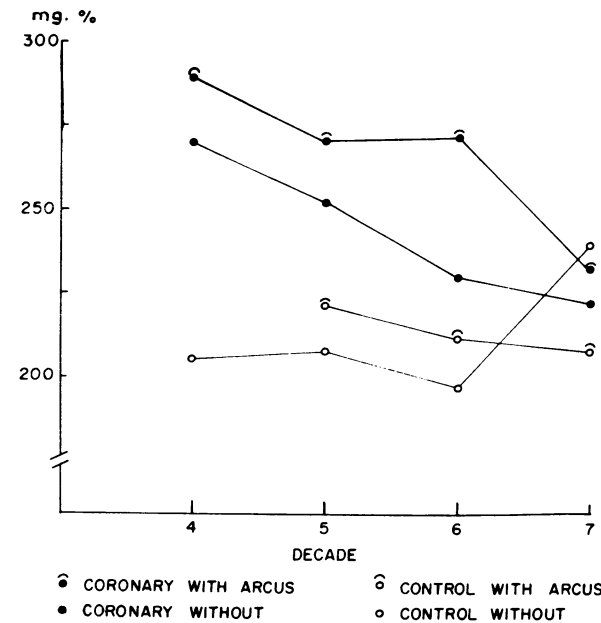


Fig. 2.—Relation of incidence of arcus to total serum cholesterol. In the fourth to sixth decades the subjects with arcus have higher mean serum cholesterol levels.

these differences in serum cholesterol. In the control group no combination of decades produced significant differences. In the coronary group, however, arcus was significantly associated with higher serum cholesterol levels in the combined fourth, fifth and sixth decades. When the coronary and control groups were combined, a significant association was present in the fourth, sixth and combined decades. In the fifth decade the association becomes significant by the one-tailed test, which can justifiably be used here.

TABLE VII.—CORNEAL ARCUS: RELATION TO SERUM LIPOPROTEINS IN CONTROL GROUP\*

Decade	Arcus	Lipoprotein Levels (mg.%)					
		0 - 12	12 - 20	20 - 100	100 - 400	12 - 400	0 - 400
5th	Without	295 ± 58	55 ± 28	87 ± 41	28 ± 14	170 ± 71	465 ± 115
	With	304 ± 45	55 ± 17	81 ± 42	35 ± 38	171 ± 82	475 ± 98
6th	Without	274 ± 44	52 ± 16	80 ± 45	23 ± 14	155 ± 69	429 ± 89
	With	298 ± 45	60 ± 34	77 ± 28	19 ± 10	156 ± 49	454 ± 82
7th	Without	285 ± 63	54 ± 23	119 ± 105	45 ± 65	218 ± 186	503 ± 232
	With	280 ± 52	48 ± 21	74 ± 66	26 ± 31	148 ± 107	428 ± 128

\*Std. S<sub>f</sub> lipoproteins, mg.%, mean and standard deviation.  
See Table II for the numbers of subjects. None of the differences is significant.

TABLE V.—p VALUES FOR DIFFERENCES IN MEAN SERUM CHOLESTEROL AND PHOSPHOLIPID IN GROUPS WITH AND WITHOUT ARCUS

Decade	Control		Coronary		Control + Coronary	
	Chol.	Phoslip.	Chol.	Phoslip.	Chol.	Phoslip.
4th	—	—	<0.4	<0.6	<0.001	<0.02
5th	<0.4	<0.3	<0.2	<0.3	<0.1	<0.1
6th	<0.2	<0.2	<0.1	<0.01	<0.01	<0.1
4th + 5th	<0.2	<0.1	<0.2	<0.3	<0.01	<0.01
4th + 5th + 6th	<0.2	<0.1	<0.01	<0.02	<0.001	<0.001

Statistical method of probability is Student's "t" test.  
For numbers of subjects see Table I. For serum cholesterol and phospholipid levels see Tables IV and VI.

It is concluded that, up to age 60, the incidence of corneal arcus is significantly related to the level of the total serum cholesterol.

### Free or Ester Cholesterol

As previously pointed out, there is a high correlation between the free to total cholesterol in both the control ( $r = 0.96$ )<sup>5</sup> and coronary patients ( $r = 0.93$ ).<sup>4</sup> Thus nothing can be gained by calculating the correlation of corneal arcus to ester or to free cholesterol when its relationship to total cholesterol has already been established.

TABLE VI.—CORNEAL ARCUS: RELATION TO SERUM PHOSPHOLIPID\*

Decade	Control		Coronary	
	No arcus	With arcus	No arcus	With arcus
4	242.4 ± 29.7	None	278.9 ± 44.0	291.1 ± 53.2
5	247.5 ± 34.8	263.2 ± 29.1	273.0 ± 19.3	286.0 ± 28.9
6	234.2 ± 20.4	250.6 ± 34.0	257.4 ± 28.5	294.0 ± 34.7
7	275.0 ± 47.0	256.1 ± 33.6	250.2 ± 28.6	256.9 ± 34.5
8	253.5 ± 36.1	254.3 ± 34.4	323.0	261.2 ± 26.6

\*Mg.%, mean and standard deviation.  
See Table II for the numbers of subjects, and Table V for the probability level.

### Phospholipid

Table VI relates the presence of corneal arcus to the levels of the serum phospholipid by decade in both groups. The data are generally similar to those presented for cholesterol in Table IV. In both groups, up to age 60, the subjects with arcus tended to have higher mean serum phospholipid levels. Only in the sixth decade of the coronary group did this reach significance (Table V). Again, by combining the decades and the groups, significant associations can be demonstrated, and the significance is improved if the one-tailed test is used.

It is concluded that, up to age 60, the incidence of corneal arcus is significantly related to the level of the serum phospholipid.

TABLE VIII.—CORNEAL ARCUS: RELATION TO SERUM LIPOPROTEINS IN CORONARY GROUP†

Decade	Arcus	0 - 12	12 - 20	20 - 100	100 - 400	12 - 400	0 - 400
4th.....	Without	436 ± 101	74 ± 22	132 ± 52	76 ± 70	278 ± 121	718 ± 191
	With	414 ± 160	76 ± 47	110 ± 71	44 ± 37	230 ± 137	644 ± 58
5th.....	Without	408 ± 87	75 ± 30	121 ± 33	47 ± 21	242 ± 59	650 ± 120
	With	408 ± 118	59 ± 13	126 ± 79	70 ± 99	256 ± 169	665 ± 163
6th.....	Without	329 ± 49	52 ± 21*	102 ± 49	46 ± 33	200 ± 98	529 ± 125
	With	359 ± 71	70 ± 19	120 ± 56	67 ± 41	256 ± 98	615 ± 144
7th.....	Without	338 ± 105	38 ± 11	71 ± 29	31 ± 14	140 ± 49	468 ± 134
	With	324 ± 40	50 ± 21	70 ± 48	28 ± 35	148 ± 95	473 ± 112

†Std. S<sub>r</sub> lipoproteins, mg.%, mean and standard deviation.

See Table II for the numbers of subjects. \*Only difference of significance.

### Lipoproteins

As shown in Tables VII and VIII, in both the control and coronary groups, there was (with a lone exception) no demonstrable relationship between the presence of corneal arcus and the concentration of any of the Std. S<sub>r</sub> serum lipoprotein fractions. Nor did any combination of decades or of subjects produce a significant association.

### RELATION OF DEGREE OF CORNEAL ARCUS TO TOTAL SERUM CHOLESTEROL

Table IX shows that in the earlier decades of both groups there was a tendency for the more severe degree of arcus to be associated with higher levels of serum cholesterol. In the older decades no correlation was present but this may be due to its being obscured by the stronger correlation between arcus and age.

TABLE IX.—DEGREE OF CORNEAL ARCUS AND SERUM CHOLESTEROL

Decade	No arcus		Slight arcus		Moderate arcus		Marked arcus	
	n	Chol.	n	Chol.	n	Chol.	n	Chol.
<i>Control group*</i>								
5th	13	208	7	205	4	241	1	260
6th	10	197	10	210	6	208	1	259
7th	5	241	4	216	9	216	5	190
8th	2	246	5	228	5	200	9	204
<i>Coronary group</i>								
4th	14	270	10	286	0	—	1	328
5th	13	252	9	272	3	233	3	296
6th	15	230	9	281	2	248	2	256
7th	4	214	7	240	6	246	5	209
8th	1	330	4	256	5	193	2	242

n = number; Chol. = total serum cholesterol, mg.%, mean.

\*No corneal arcus in fourth decade of control group.

### RELATION OF INCIDENCE OF CORNEAL ARCUS TO INCIDENCE OF ABDOMINAL AORTIC CALCIFICATION

The demonstration of calcification of the abdominal aorta by roentgenography employing the spine technique is usually taken as proof of advanced atherosclerosis of the aortic wall.<sup>9</sup> Table X shows that in both the control and coronary groups there was no apparent relationship between the presence of corneal arcus and abdominal calcification.

TABLE X.—CORNEAL ARCUS: RELATION TO ABDOMINAL CALCIFICATION

Decade	Control			Coronary		
	Arcus	Calcification	Both	Arcus	Calcification	Both
4th	0	0	0	11	0	0
5th	12	1	1	15	8	4
6th	17	7	3	13	7	1
7th	18	6	3	18	15	13
	47	14	7	57	30	18

See Table II for the numbers of subjects.

### DISCUSSION

Arcus is a peripheral greyish-white opacity of the corneal stroma. Synonyms include arcus senilis, arcus pinguis, arcus lipoides and gerontoxon. If it appears in early life, it is known as arcus juvenilis, arcus pre-senilis or arcus senilis praecox.

Histologically, fat stains show the lipid material of the arcus to be concentrated in two wedges adjacent to Bowman's and Descemet's membranes, with the apices directed toward the midstroma. The lipid droplets are mainly intracellularly, with lesser amounts extracellularly. In Bowman's membrane, the droplets are arranged most densely at the peripheral limits, producing the sharp edge seen clinically. In the substantia propria the globules occur both in and between the lamellae, in the corneal corpuscles, and particularly in large foamy histiocytic cells found in all the layers.<sup>7</sup>

The initial stage of human corneal arcus, as demonstrated by the use of the biomicroscope, is decreased transparency and a granular appearance in the periphery of the cornea.<sup>6, 10</sup> Clinically, it is first evident as a peripheral ring of haze in the lower and upper parts of the cornea. Each opacity grows until eventually the two fuse circumferentially to form a complete annulus. The end result appears as a ring of opacity separated from the limbus by a clear zone, the lucid interval of Vogt. It is limited by a sharp line on the outer limbal edge and shades off gradually towards the inner edge, but never approaches the pupillary zone. The condition tends to be bilaterally symmetrical.

Corneal arcus is quite innocent. There are no associated symptoms or disturbances of vision, and no treatment is required. Arcus develops earlier in the male and there is a rapid increase in incidence

with middle age. Duke-Elder<sup>7</sup> noted its constant occurrence in later life and considered it "essentially a simple senile degeneration coming into the same category as atherosclerosis and presumably depending on partial and progressive obliteration of the capillary system at the limbus". It can develop in youth as the result of local premature changes secondary to constant exposure to irritating dusts and chemicals, or secondary to corneal disease such as interstitial keratitis. In the latter case it may thus be uniocular.

A relation of corneal arcus to serum cholesterol is suggested by its frequent occurrence in patients with familial hypercholesterolemia. As early as 1911, high cholesterol levels were reported in persons with arcus,<sup>11</sup> but most later investigators did not confirm this association.<sup>6</sup> The significant correlation of arcus to serum cholesterol in our coronary patients is similar to that reported by Boas and Adlersberg.<sup>12</sup> In healthy subjects too, it has recently been found that to age 60, serum lipids are elevated in those with arcus.<sup>6, 13</sup> Over this age, as in our study, no relation could be demonstrated.<sup>6, 14</sup> The relation of arcus to high serum cholesterol may not, however, be a direct one. Thus, arcus is seldom seen in persons with hypothyroidism;<sup>15</sup> and arcus is more frequent (but xanthelasma less frequent) in men than in women.<sup>6</sup>

The connection between corneal arcus and arteriosclerosis has been controversial for over a century. Our data agree with the prevailing opinion that the incidence of arcus and of CHD both increase with age but there is no correlation after 40.<sup>6, 16, 17</sup> The important finding of this study is that under 40, corneal arcus was the only physical sign that distinguished our coronary patients from the controls. The 44% incidence reported here is considerably higher than that previously documented in young coronary groups.<sup>18, 19</sup> On the other hand, Forsius,<sup>6</sup> in a meticulous study that included biomicroscopic examination, found a slight degree of arcus to be visible macroscopically in 19 of 51 normal Finnish men in the fourth decade. Unfortunately, he did not study a coronary group.

Thus, the clinical prevalence of corneal arcus may depend not only on the method of examination but on the population studied. It does appear, however, that the prevalence of arcus is significantly increased in younger coronary patients. From a clinical viewpoint, arcus can be accepted as an isolated change of no real significance when it appears in the aged. However, its presence in men under 40 should arouse suspicion of the possibility of hypercholesterolemia and a propensity to CHD.

Many similarities between corneal arcus and clinical atherosclerosis can be found. The incidence of both increases rapidly after 40. The same kind of patient is involved: male, mesomorph<sup>6</sup> and of a driving personality.<sup>20</sup> Both are common in conditions such as familial xanthomatosis, diabetes and nephrosis in which hyperlipidemia is frequent.<sup>6</sup> Subjects with coronary atherosclerosis and subjects

with corneal arcus both have higher than average serum cholesterol levels. The two lesions can be produced by feeding experimental animals a high cholesterol diet.<sup>6</sup> Pathologically, both can be initiated by local disease, e.g. atherosclerosis by syphilis, and arcus by keratitis. Cogan and Kuwabara<sup>21</sup> suggested that a pathological analogy can be drawn between arcus in the cornea and diffuse sudanophilia in the intima. In either site the fatty tissue may stimulate vascularization.<sup>6</sup>

Finally, these data linking coronary atherosclerosis, corneal arcus and the level of the serum lipids could be interpreted as providing further evidence for the lipid theory of atherogenesis.

#### SUMMARY

The relation of corneal arcus to atherosclerosis and to serum lipids was investigated in men with coronary heart disease and in healthy controls.

The incidence of arcus after the fourth decade was similar in both groups. Under 40, there was a striking difference: arcus was present in 11 of the 25 coronary patients and in none of the controls. In both groups, to age 60, arcus was positively correlated to the concentrations of serum cholesterol and phospholipid but not to lipoproteins. The coronary group, to age 60, had significant elevation of the serum lipids and lipoproteins.

Since arcus is itself a fatty infiltration of the eye, these findings support the lipid theory of atherogenesis. Clinically, the presence of a corneal arcus in a man under 40 may be a clue to hyperlipidemia and a propensity to coronary heart disease.

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