

the public sector. This might include STD treatment, for example. If the local or provincial government is paying for a service, it has the right to ensure that the service is of acceptable standard? Other options include making STD drugs or STD syndrome packets available to the private sector at state tender prices. There is always a risk of abuse, but with correct organisation and auditing, abuse could be minimised.

#### Education

Education of doctors and other health workers needs to start with the undergraduate curriculum. Education needs to continue through specialist and postgraduate training, and also to be complemented by a programme of continuing medical education thereafter. Today's health worker needs to understand the value of evidence-based medicine, standard treatment guidelines, and structured approaches to care.

#### CONCLUSION

STD control must remain a high priority for South Africa. Achieving control is unlikely if the public sector acts alone.15 Many patients seek care in the private medical sector and an effective partnership between it and the public sector needs to be forged. While quality of services can be assessed locally, it seems likely that effective change will only occur within a framework of legislation, financial incentives and continuing education.

- Abdool Karim SS. Challenges to the control of sexually transmitted diseases in Africa. Am I Public Health 1994; 84: 1891-1893.
- Gerbase A, Rowley J, Heymann D, Berkley S, Piot P. Global prevalence and incidence
- estimates of selected curable STDs. Sex Transm Infect 1998; 74: suppl 1, S12-S16. UNAIDS. AIDS Epidemic Update: December 1998. Geneva: UNAIDS, 1998.
- Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet 1995; 346: 530-536.
- 530-536. World Bank. World Development Report, 1993. Washington, DC: World Bank, 1993. Ward H, Mertens T, Thomas C. Health seeking behaviour and the control of sexually transmitted disease. Health Policy and Planning 1997; 12: 19-28. Garcia P, Gotuzzo E, Hughes J, Holmes K. Syndromic management of STDs in pharm.
- ent of STDs in pharmacies
- evaluation and randomised intervention trial. Sex Transm Infect 1998; 74: suppl 1, S153-S158. Wilkinson D, Abdool Karim S, Harrison A, et al. Unrecognised sexually transmitted infection 8. in rural South African women - the hidden epidemic. Bull World Health Organ 1999; 77: 22-
- 9. Coleman RL, Wilkinson D. Increasing HIV prevalence in a rural district of South Africa from
- 1992 through 1995. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 16: 50-53.
   Wilkinson D, Connolly AM, Harrison A, Lurie M, Karim SS. Sexually transmitted dis syndromes in rural South: results from health facility surveillance. Sex Transm Dis 1998; 25(1): 20-23.
- Connolly A, Wilkinson D, Harrison A, Lurie M, Abdool Karim S. Inadequate treatment for STDs in the South African private health sector. Int J STD AIDS 1999; 26: 152-156.
- 12. Harrison A, Wilkinson D, Lurie M, Connolly A, Abdool Karim S. Improving quality of STD
- case management in rural South Africa. AIDS 1998; 12: 2329-2335.

  13. Wilkinson D, Harrison A, Lurie M, Abdool Karim S. STD syndrome packets: improving
- syndromic management of sexually transmitted diseases in developing countries. Sex Trans. Dis 1999; 26: 152-156. 14. Harrison A, Abdool Karim SS, Floyd K, et al. Syndrome packets and health worker training
- improve quality of sexually transmitted disease case management in rural South Africa: results of a randomised controlled trial. AIDS 2000; 14: 2769-2779.
- Dartnall E, Schneider H, Hlatshwayo Z, Clewes F. STD Management in the Private Sector: A National Evaluation, (CHP Technical Report TK31). Johannesburg: Centre for Health Policy, University of the Witwatersrand, 1997: 45.

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## CORTICAL LENS OPACITIES IN THE YOUNG PATIENT — AN INDICATION FOR A LIPOGRAM?

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Aim. To determine the characteristics and prevalence of lenticular opacification in patients with underlying dyslipidaemia.

Methods. Eighty patients of both genders and all ages (18 - 90 years) were enrolled in the trial if they met the inclusion criteria for dyslipidaemia.

Patients were included if their fasting serum cholesterol and triglyceride concentrations were > 5.2 mmol/l and > 2.3 mmol/l, respectively, when measured on three separate occasions over a 1-month period.

Patients were excluded if they suffered from any condition known to cause or predispose them to elevated lipid levels or lenticular opacification. Lenticular changes were assessed by means of a slit-lamp through the fully dilated pupil and other physical signs were documented subsequent to thorough physical evaluation.

Results. In addition to the classic clinic signs of dyslipidaemia, 31% of patients had cortical lens opacities. Cortical opacities were twice as prevalent as Achilles tendon thickening (16.3%) in our study, the second most prevalent sign of elevated lipid levels. In the subgroup of patients aged under 50 years, 55% had lenticular opacities, predominantly cortical (80%).

Conclusions. Cortical lens opacification was the most prevalent sign of dyslipidaemia and it occurred at a relatively young age in our trial population in those patients who were affected. Cortical lenticular opacification should be regarded as an indication for blood lipid profile evaluation.

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Lens opacification<sup>1</sup> and cardiovascular disease<sup>2</sup> are two of the main causes of morbidity worldwide. Lens opacity, manifesting as cataract, is responsible for an estimated 40% of the 42 million cases of blindness in the world.<sup>3</sup> Heart disease, on the other hand, is the single greatest cause of death in developed countries.<sup>4</sup> The relationship between cholesterol and cardiovascular heart disease is well documented.<sup>5-10</sup> The relationship between cholesterol and lens opacity is, however, far less well appreciated.

Issues relating to drug safety and inherited defects in enzymes mediating cholesterol metabolism have brought renewed attention to a possible interrelationship between lipid metabolism and cataract induction in humans. The lens is unique in that it contains a relative abundance of cholesterol in the fibre cell plasma membrane<sup>11</sup> and furnishes its needs for the latter by on-site biosynthesis.<sup>12</sup> It has been shown that inhibition of cholesterol synthesis in the lens leads to cataract formation in humans.<sup>13</sup>

The Smith-Lemli-Opitz syndrome, <sup>12-15</sup> mevalonic aciduria <sup>16</sup> and cerebrotendinous xanthamathosis <sup>17,18</sup> are inherited disorders of cholesterol metabolism and affected patients may present with lens opacities. Triparanol, a hypolipidaemic agent that inhibits cholesterol biosynthesis, was withdrawn from clinical use because of its propensity to induce cataract formation in humans. <sup>19,20</sup> The very widely used vastatin class of hypolipidaemic medicines are potent inhibitors of cholesterol biosynthesis and are able to lower serum lipid concentration effectively. <sup>21,22</sup> Although high ocular safety in older patients over periods of up to 5 years has been reported, <sup>22-29</sup> it is still not clear whether these agents have the potential to be cataractogenic, particularly in younger patients and over longer periods. The vastatins have been reported to lower mortality effectively in dyslipidaemic patients suffering from heart disease. <sup>30,34</sup>

In order to assess the prevalence of lenticular opacities in patients with dyslipidaemia (raised serum cholesterol and triglycerides), a group of 80 dyslipidaemic patients were subjected to general physical examination and an ophthalmic examination of the fully dilated eye.

### **METHODS**

In order to obtain a study group with maximum homogeneity only patients meeting the following inclusion criteria were enrolled: (i) male or female (18 - 90 years of age); (ii) high serum total cholesterol (> 5.2 mmol/l); (iii) low high-density lipoprotein (HDL) cholesterol (< 1.8 mmol/l); and (iv) high triglycerides (> 2.3 mmol/l).

Exclusion criteria were: (i) pregnant or lactating women; (ii) severe hypertension (diastolic blood pressure (BP) > 115 mmHg); (iii) history of cardiovascular disease; (iv) diabetes mellitus (fasting blood glucose > 7.8 mmol/l); (v) hypothyroidism, defined as thyroid-stimulating hormone

(TSH) > 7.5 mU/l; (vi) any malignant tumour; (vii) significant renal impairment (serum creatinine > 170 µmol/l); (viii) history of pancreatitis; (ix) patient with gallbladder disease, including cholelithiasis; (x) history of gastro-intestinal disease; and (xi) HIV antibody-positive.

Fasting blood samples were obtained from each individual on three occasions over a period of 4 weeks. Patients were only included in the study if their lipid variables adhered to the inclusion criteria on each of the three visits.

All classic physical signs of abnormal lipid variables were documented, namely: (i) xanthomas (on the Achilles tendon, hands, elbows or knees); (ii) palmar yellow striae; (iii) xanthelasma; and (iv) corneal arcus.

Lenticular opacities were classified as being cortical, nuclear or subcapsular on the basis of the characteristics and grading as indicated below:

- 1. Cortical opacities: (i) water clefts, vacuoles, and flakes none, few, moderate, or many; (ii) wedges and spokes involving 1, 2, 3 or 4 quadrants; and (iii) maximal inward extension minimal, moderate or advanced.
- Nuclear opacities: (i) tissue discoloration normal colour, pale yellow, yellow, dark yellow or brown.
- 3. Subcapsular opacities: (i) posterior capsule involvement graded 1 4; and (ii) anterior capsule involvement graded 1 4.

A specialist physician and an ophthalmologist examined all the patients.

#### RESULTS

Eighty patients were analysed and Table I reflects their demographic data.

Variable	Mean	Standard deviation
Age (yrs)	53.9	± 11.8
Blood pressure (mmHg)		
Systolic	134	± 18
Diastolic	84	±9
Body mass index (kg/m²)	28.29	± 4.82
	Number (%)	
Race		
Mixed race	15 (18.8)	
Caucasian	65 (81.3)	
Gender		
Male	48 (60)	
Female	32 (40)	_
Smokers		
Present	23 (27.5)	
Past	34 (42.5)	
Never	23 (27.5)	No E Total
Alcohol consumer	55 (68.8)	A STATE OF THE STA



**52**1



Most of the study group patients were male, Caucasian and smokers. Most patients (68.8%) admitted to regular alcohol consumption. The mean systolic and diastolic BP data, 134 mm Hg (standard deviation (SD) 18 mmHg) and 84 mmHg (SD 9 mmHg), respectively, fell within the normal range for age. The body mass index (BMI) of the group was significantly greater than the norm, i.e. 28.89 kg/m² (SD 4.82 kg/m²).

Fig. 1 depicts the serum lipid variables. Patients were included in the study only if total serum cholesterol was > 5.2 mmol/l when measured on three separate occasions over a 4-week period, and low-density lipoprotein (LDL) and HDL were uniformly > 2.3 mmol/l and < 1.8 mmol/l, respectively.

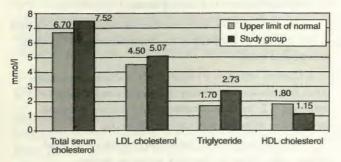


Fig. 1. Serum lipid parameters of the study group (N = 80) compared with the upper limit of normal (mmol/l).

The prevalence of lenticular opacities divided the study group into two cohorts, i.e. those with normal lenses (62%) and those with opacities (39%) (Fig. 2).

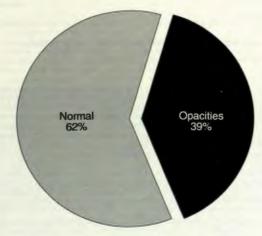


Fig. 2. Prevalence of lens opacities in the study group.

### Subgroup results

Comparative analysis with regard to age, BP, BMI, lipid index and uric acid profile did not reveal significant differences between the two subgroups (Table II).

The prevalence of lenticular opacity in dyslipidaemic patients in the 30 - 40-year age group was 33%. This age group was not studied in the Barbados Eye Study (BES)<sup>36</sup> or the

Table II. Comparison of subgroup with normal lenses (61%) and the subgroup with lenticular opacities (39%)

Variable	Normal (mean (± SD))	Opacity (mean (± SD))	
Age (yrs)	55.3 ± 10.9	54.7 ± 14.8	
Blood pressure (mmHg)			
Systolic	$135.6 \pm 21.19$	140.0 ± 21.81	
Diastolic	84.4 ± 10.03	$86.1 \pm 9.83$	
Body mass index (kg/m²)	28.55 ± 4.84	27.81 ± 4.84	
Total cholesterol (mmol/l)	$7.3 \pm 2.01$	$7.91 \pm 2.00$	
LDL cholesterol	$5.05 \pm 1.54$	5.11 ± 1.46	
HDL cholesterol	$1.16 \pm 0.39$	$1.14 \pm 0.31$	
Triglycerides	2.64 ± 1.89	$2.89 \pm 1.02$	
Uric acid (mmol/l)	$3.64 \pm 0.91$	3.98 ± 1.25	

Beaver Dam Eye Study (BDES),<sup>36</sup> and consequently data for comparison are not available. In the 40 - 50-year age group the prevalence of lenticular opacity in our patients was 50% compared with 4.7% in the BES and 8.3 in the BDES. Differences in the older age groups were not prominent (Table III, Fig. 3).

Table III. Age distribution of patients with opacities compared with other population-based studies

Age group	Percentage of opacities			
(yrs)	Study group	BES**	BDES*	
30 - 40	33.33	N/A	N/A	
40 - 50	50.00	4.7	8.3	
50 - 60	18.51	24.5	26.5	
60 - 70	33.33	57.5	56.7	
70 - 80	66.67	85.9	70.5	
80+	33.33	98.3	N/A	

100 Study group 80 BES3 ☐ BDES36 Percentage 50% 40 25% 27% 20 o 30 - 4060 - 70 40 - 50 50 - 60 70 - 80 Age groups (vrs)

Fig. 3. Age distribution and percentage of patients with opacities compared with other population-based studies.

No lateralising bias was observed in the subgroup with lenticular opacities (Fig. 4). This is supported by the findings in normal clinical practice, where a predilection for laterality of age-related cataracts does not exist.

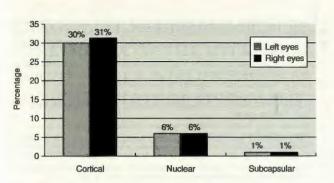


Fig. 4. Types of opacities compared with laterality.



Modern medicine today aspires to the early detection of disease processes, with the aim of early intervention in an attempt either to halt the progression or to reverse the process.

Although the classic systemic signs of dyslipidaemia are well appreciated, i.e. xanthomas, xanthelasma, thickening of the Achilles tendon and corneal arcus, in our study the prevalence of one or more of the ocular signs was far greater than that of the systemic signs — 47.3% for the former as opposed to 23.8% for the latter.

The distribution of dyslipidaemia-related signs in our patients was as follows: xanthelasma (7.5%), corneal arcus (8.8%), Achilles tendon involvement (16.3%), and cortical lenticular opacity (31.0%).

It is noteworthy that the most frequent ocular sign, cortical lenticular opacity, occurred twice as frequently as the most frequent systemic sign, Archilles tendon thickening (Fig. 5).

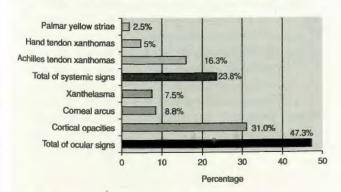


Fig. 5. Physical signs associated with dyslipidaemia.

Although a control group of patients was not evaluated simultaneously, valid comparisons could be made between our data and those of other population-based studies. In the BDES\* and the BES,\* 40% and 41% of the patients, respectively, had lens opacities compared with 39% in our dyslipidaemic patients.

Fig. 6 compares the prevalence of the different morphological subtypes of opacities in our study and in the

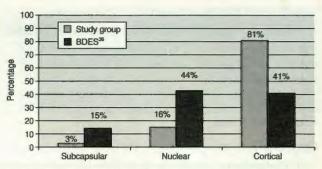


Fig. 6. Prevalence of the morphological types of opacities in our study group vs. the BDES.\*\*

BDES.\* It is clear that cortical opacities occurred twice as frequently in the hyperlipidaemic group as in the normal population, whereas nuclear opacities occurred with more than twice the frequency in the normal population.

The mean age of our patients was  $53.9 \pm 11.8$  years, and not surprisingly the prevalence of nuclear cataracts was relatively low. Since nuclear degeneration correlates strongly with age and ageing, it is more prevalent in the elderly. In contrast, cortical lens opacities were highly prevalent in our study group.

Patients with conditions known to induce lens opacification, e.g. diabetes mellitus, neoplastic disease, hypothyroidism, pancreatitis, renal failure, severe hypertension and HIV/AIDS complex, among others, were meticulously excluded from the trial. Maritz<sup>®</sup> has shown that dyslipidaemic patients have a higher risk of developing adult-onset diabetes mellitus with advancing age than the general population. No patient in the study group had a fasting blood glucose concentration in excess of 7.8 mmol/l, and consequently it is highly unlikely that hyperglycaemia contributed to the high prevalence of cortical opacification.

Most of the patients in the BES<sup>38</sup> were black, and the comparative data from the trial appeared to reveal that black people are at greater risk of developing cortical opacities than Caucasians, and that the latter in turn are at greater risk of developing nuclear opacities.

In contrast to the BES, most of our patients were Caucasians (85%), the rest all being individuals of mixed race. It is possible that capsular opacities are equally prevalent in black and white people and our data provide sufficient motivation for further assessment of this factor in the aetiology of lens opacification.

Defining a cataract is difficult. Harding defines it as 'An opacification of the ocular lens sufficient to impair ocular vision.' We have deliberately steered away from the term cataract because most of the lens changes were not cataracts according to the Harding definition, but rather lenticular opacities as described by the Lens Opacities Classification System II (LOCS II). None of the observed opacities was

523





severe enough to cause substantial visual impairment.

It has been reported that corneal arcus represents a reliable sign of dyslipidaemia only in patients under 50 years of age and that 60% of patients with periocular xanthelasma are normolipidaemic.40

#### CONCLUSIONS

Our conclusions are as follows:

- 1. Dyslipidaemic patients are more likely to develop cortical opacification than the normal population.
- Cortical lens opacification manifests at a younger age than does nuclear opacification.
- 3. It is essential that an abnormal lipid profile be diagnosed or detected as early as possible in order to achieve the maximum possible benefit from therapeutic intervention.
- 4. Cortical lens opacification in the patient younger than 50 years of age should alert the ophthalmologist to arrange for diagnostic serum lipid assessment.
- 5. The young patient with dyslipidaemia should undergo regular slit-lamp examination of the lens after full dilatation of the pupil in order to detect early signs of lens opacification.
- 6. Cortical lenticular opacification should be regarded as one of the most common, and hence reliable, clinical signs of dyslipidaemia.

- World Health Organisation. Management of Cataracts in Primary Health Care Services. Geneva: 1. WHO, 1990.
- Epstein FH. Cardiovascular disease epidemiology; A journey from the past into the future. Circulation 1996; 93: 1755-1764.
- Hyman L. Epidemiology of eye disease in the elderly. Eye 1987; 1: 330-341.
- Assmann G, ed. Lipid Metabolism Disorders and Coronary Heart Disease. Munich: MMV-Medizin-Verl., 2nd ed., 1993.
- Cooperative Study of Lipoproteins and Atherosclerosis. Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Circulation 1956: 14: 691-741.
- Dawber TR. The Framingham Study: The Epidemiology of Atherosclerotic Disease Cambridge/London: Harvard University Press, 1980.
- 7. Gofman PA, Spector C. The role of lipids and lipoproteins in atherosclerosis. Science 1950;
- Keys A. Atherosclerosis: a problem in newer public health. J Mt Sinai Hosp 1953; 20: 118-139.
- Law MR, Wald NJ. An ecological study of serum cholesterol and ischaemic heart disease between 1950 and 1990. Eur J Clin Nutr 1994; 48: 305-325.
- Simons LA. Interrelations of lipids and lipoproteins with coronary artery disease mortality in 19 countries. Am J Cardiol 1985; 57: 5G-10G.
- 11. Cenedella RJ. Cholesterol and cataracts. Surv Ophthalmol 1996; 40: 320-337.
- 12. Cotlier E, Rice P. Cataracts in the Smith-Limli-Opitz syndrome. Am J Ophthalmol 1971; 72: 955-
- 13. Finley SC. Finley WH, Monsky DM. Cataracts in girl with features of Smith-Lemli-Opitz syndrome. J Pediatr 1969; 75: 706-707.
- Kretzer FL, Hittner HM, Mehta RS. Ocular manifestations of the Smith-Lemili-Opitz syndrome. Arch Ophthalmol 1981; 99: 2000-2006.
- Tint GS, Irons M. Elias ER. Defective cholesterol biosynthesis associated with the Smith-Lemli-Opitz syndrome. N Engl J Med 1994; 330: 107-113.
- Hoffman G, Gibson KM, Brandt IK. Mevalonic aciduria: An inborn error of cholesterol and nonsterol isoprene biosynthesis. N Engl J Med 1986; 314: 1610-1614.
- Björkhem I, Boberg KM. Inborn errors in bile biosynthesis and storage of sterols other than cholesterol. In: Scriver CR, Beaudet AL, Sly WE, Valle D, eds. Metabolic Basis of Inherited Disease. 7th ed. New York: McGraw-Hill, 1995; 2073-2099.
- 18. Kuriyama M, Fujiyama J, Yoshidone H, Chang Y. Cerebrotendinous xanthomatosis: clinical and biochemical evaluation of eight patients and review of literature. J Neurol Sci 1991; 102:
- 19. Kirby TJ, Achor RWP, Perry HO, Winkelman RK. Cataract formation after triparanol therapy.

- 20. Laughlin RC, Carey TF. Cataract in patients treated with triparanol. JAMA 1962; 181: 339-340.
- 21. Gretton C. Like fallling off a cliff. Medical Advertisement News 1994: 5: 3-25.
- 22. Grundy SM. HMG-KoA reductase inhibitors for treatment of hypercholesterolaemia. N Engl J Med 1988; 319: 24-33.
- 23. Boccuzzi SJ, Bocanegra TS, Walker JF. Long-term safety and efficiency profile of simvastatin. Am J Cardiol 1991; 68: 1127-1131.
- 24. Havel RJ, Hunninghake DB, Illingworth DR. Lovastatin (Mevolin) in the treatment of heterozygous familial hypercholesterolemia. Ann Intern Med 1987; 107: 609-615.
- 25. Hunninghake DB, Miller, VT, Goldberg I. Lovastatin: Follow up ophthalmological data. JAMA 1988; 259: 354-355.
- 26. Lovastatin Study Group II: Therapeutic response to lovastatin (mevolin) in non-familial hypercholesterolemia. JAMA 1988; 260: 359-366.
- Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. JAMA 1988; 260: 359-366.
- 28. Lovastatin Studygroup IV. A multicenter comparison of lovastatin and probucol for treatment of severe primary hypercholesterolemia. Am J Cardiol 1990; 66: 22B-30B
- 29. Tobert JA. New developments in lipid-lowering therapy: the role of inhibitors of hydroxymethylglutaryk-coenzyme A reductase. Circulation 1987; 76: 534-538
- 30. Holme I. Statinbehandeling ved hoy risiko for koronarsykdom. Tidasskr Nor Laegerforen 1996;
- 31. Nigg C. Die 4-S-Studie ein Wendepunkt in der Cholesterindiskussion. Schweiz Rundsch Med Prax 1995; 84 (51-52): 1514-1516.
- 32. Olsson AG. Ny hyperkolesterolemistudie; Statin effaktivt mot hjartsjukdom. Lakartidningen 1996; 93: 2131-2133.
- 33. Samani JN, de Bono DP. Prevention of coronary heart disease with pravastatin. N Engl J Med 1996; 334: 1333-1334
- 34. Windler E. HMG-KoA Reduktasehemmer zur Pravention und Behandlung der KHK. Fortschr Med 1996: 114: 89-90.
- 35. Leske MC, Connel AMS, Schadat A. Prevalence of lens opacities in the Barbados Eye Study. Arch Ophthalmol 1997; 115: 105.
- 36. Klein BEK, Klein R, Lee KE. The incidence of age-related cataract, the Beaver Dam Eye Study. Arch Ophthalmol 1998; 116: 219.
- 37. Maritz FJ. Aspects of dyslipidaemia in diabetes mellitus. S Afr Med J 1997; 87: 373-377.
- 38. Harding J. Cataract: Biochemistry, Epidemiology and Pharmacology. London: Chapman and Hall,
- Chylack LJ jun. Leske MC, Mc Carthy D, Khu PM, Kashiwagi T, Sperduto R. Lens opacities
- classification system II (LOCS II). Arch Ophthalmol 1989; 107: 991-997.

  Munro J, Edwards E. Macleod's Clinical Examination. London: Churchill Livingstone, 1995.

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