NS 1392422 (autor)

the Farnsworth-

ope examination
rchive for Clinical

on. *Journal of the*

mal ranges of the
93, 635–42.
ıorioretinopathy.

rophic hormone
9–44.

CHAPTER 42

EARLY VISION LOSS IN DIABETIC PATIENTS ASSESSED BY THE CAMBRIDGE COLOUR TEST

D. F. VENTURA, M. F. COSTA, M. GUALTIERI, M. NISHI, M. BERNICK, D. BONCI, AND J. M. DE SOUZA

Introduction

Colour vision is one of the visual functions severely affected by Type II *Diabetes mellitus* (DMII). Colour vision loss occurs when there is diabetic retinopathy (Remky *et al.* 2000) and is proportional to the degree of retinopathy (Tregear *et al.* 1994, 1997). Colour contrast sensitivity is affected in peripheral vision in the early stages of retinopathy, whereas central (macular) loss is proportional to the stage of the pathology (Fristrom 1998).

These losses have been attributed to vascular changes related to diabetes and not much attention has been paid to the possibility that they may represent neural changes in addition to circulatory ones (Lieth *et al.* 2000). Recent research with various different methods and situations has confirmed that even before the onset of diabetic retinopathy there is colour vision loss (Deschenes *et al.* 1997; Ismail and Whitaker 1998; Kurtenbach *et al.* 2000; North *et al.* 1997*a*) and reduction in contrast sensitivity (North *et al.* 1997*b*). Colour vision may be assessed by different tests and a battery of tests is recommended (Birch 1993) since they measure different aspects of visual function.

A recently released test (Mollon and Reffin 2000) is the Cambridge Colour Test (CCT), from Cambridge Research Instruments, developed by Mollon and Reffin (1989) and clinically adapted by Regan *et al.* (1994). It is a computerized test that uses a psychophysical procedure to estimate MacAdam ellipses, and thus presents quantifiable results (MacAdam 1943).

There is great interest in testing colour vision with the use of a sensitive instrument that gives quantifiable results, since it may allow detection of losses not identifiable with other tests, both in the initial diagnosis and in the follow up of the condition. In DMII, as in any pathology that affects colour vision, better assessment of the losses may result in a more effective therapeutic action.

AC

We therefore used the Cambridge Colour Test to measure colour vision in diabetic patients with clinically normal fundi and in age-matched controls and compared the results with those obtained with other traditionally used tests.

Methods

Subjects

Colour vision was assessed in 9 type II *Diabetes mellitus* (DM II) patients, age 42–76 years, (mean = 60; SD = 11.3) without retinopathy, referred by the Diabetes unit of the University Hospital of the University of São Paulo. Times since DM II diagnosis ranged from 3 months to 14 years. An age-matched group of 9 non-diabetic subjects aged from 48 to 71 years (mean = 60; SD = 9.8) served as control. These Ss were selected from a group of 17 non-diabetic controls because they exceeded the tritan limit of $150 \times 10^3 u'v'$ units in the Trivector test, as was also the case of the diabetic patients. Accordingly, they were tested in the Tritanopic Set, as specified in the test manual.

All patients had received ophthalmologic evaluation within a month of colour vision testing. Diabetic patients and control subjects had VA of 1.0, except for one case, for each group, with VA of 0.9.

Colour vision was assessed monocularly in all patients and binocularly in the controls, with the best corrected visual acuity. The patients and the controls were also submitted to the Farnsworth-Munsell 100-hue test (FM 100), to the Lanthony desaturated test, and to the D15 test. An illumination of 1.49×10^3 lux was provided by two fluorescent lamps (Sylvania Octron 6500K FO32W/65K) placed 60 cm above the work surface.

Cambridge Colour Test

We used the commercial version of the Cambridge Colour Test, CCT v2.0, run on a microcomputer (Dell systems) with the VSG 5 graphics card, and a Sony FD Trinitron colour monitor (Cambridge Research Instruments).

The visual stimuli consisted of a target—the letter "C"—on a background of different chromaticity (for details see Mollon and Reffin 1989, 2000). As in the Ishihara test, both were made up of small disks of variable size and luminance. During each trial, the background chromaticity was fixed while the colour of the target was changed in order to determine a discrimination threshold, according to a psychophysical procedure (see below). The opening of the "C" was presented in four orientations (up, down, left, or right). Subjects indicated the position of the opening by pressing the correspondingly situated key on a button box.

The CCT offered two testing situations: the Trivector test and the Ellipses test, each described in detail in an accompanying manual (Mollon *et al.* 2000) and in previous publications (Mollon and Reffin 1989; Regan *et al.* 1994, 1998). The Trivector is a short test, used for rapid screening, in which discrimination thresholds relative to a background chromaticity (0.1977, 0.4689 in $u'v'$ 1976 CIE colour space) are determined in three axes or vectors in colour space: the protan, the deutan and the tritan axes.

The second testing situation, the Ellipses Test, measures three MacAdam ellipses that can be 8, 12, 16, or 20 equally spaced vectors in the CIE colour space. In our groups the 8 vector ellipses were used because the age group tired very easily. The $u'v'$ coordinates for the background chromaticity of each ellipse were: Field 1: 0.1977, 0.4689; Field 2: 0.1925, 0.5092; Field 3: 0.2044, 0.416. For subjects that exceeded a threshold distance of $150 \times 10^3 u'v'$ units in the tritan axis of the Trivector test, the ellipses were determined along a red-green axis, in a Blue–Yellow Deficiency Set—Field 1: 0.1977, 0.4689; Field 2: 0.158, 0.4738; Field 3: 0.2422, 0.4634. The software compiled the subject's responses, automatically plotted the threshold for each vector and fitted an ellipse through the thresholds centred on the background colour.

Tests with the CCT were performed in a darkened room, with the computer monitor screen off or dimmed. The subject was positioned 3 m away from the stimulus monitor. The short test version, the Trivector, was determined first, for screening purposes. Eight-vector ellipses were determined. The results were expressed in $u'v'$ coordinates in CIE colour space.

Psychophysical procedure

The CCT used the staircase psychophysical method for threshold determination, presenting two staircases in random alternation. Each staircase began with a saturated hue and proceeded to a less saturated hue every time the S made a correct response. Conversely, an incorrect response or no response was followed by presentation of hues with higher saturation value. Step size was halved or doubled, following correct or incorrect responses, respectively. After six incorrect responses or six reversals, the staircase was terminated and a threshold was computed. Successively, other pairs of hues were tested.

Results

Consistent results were obtained from all Ss, regardless of the lack of preliminary training or the education level. When patients had difficulty understanding the procedure the tester repeated the instructions and allowed a short period of training.

Compared with control Ss (Table 42.1), all patients presented some degree of colour vision loss in the CCT (Table 42.2), ranging from a slight tritan loss (4/18 eyes) to a large tritan loss (4/18 eyes) and from a small to a major diffuse loss (respectively, 7/18 and 1/18 eyes).

Diabetic patients had differences between the two eyes in Trivector thresholds, with the better eye close to age-matched control thresholds and the worst eye showing elevated thresholds (Fig. 42.1). The protan and deutan thresholds were significantly different from those of the controls ($p < 0.005$) but the tritan thresholds were not.

Average ellipse area and length also had much larger values in the worst eye of diabetic patients than in age-matched controls, whereas the angles were close to those of age-matched controls (Fig. 42.2). The fact that DM II ellipses had a narrow distribution of angles, close to 90°, might reflect a tritanopic trend. However, this was not a general rule.

Table 42.1 Test results for age-matched non-diabetic subjects

ID	Age	Eye	Lanthony	FMH100	Trivector test			Ellipses test		
					P	D	T	F1	F2	F3
P. R. S.	48	Both	Normal	36	82	71	163	(32.4, 3.4) 92	(31.6, 2.1) 87	(22.5, 2.5) 43
C. A. S.	49	Both	Normal	52	68	79	236	(39.9, 2.5) 86	(48.4, 2.0) 99	(42.1, 1.5) 88
M. S. F.	54	Both	—	36	120	87	196	(32, 2.0) 89	(37.2, 1.8) 95	(29.8, 2.2) 88
H. R. J.	55	Both	Normal	36	44	51	167	(18.3, 3.2) 102	(29.9, 2.5) 89	(27.3, 2.6) 77
Z. B. N.	55	Both	Normal	52	62	100	173	(25.6, 4.1) 79	(34.2, 2.5) 105	(26.8, 1.9) 55
M. T. A. S.	63	Both	Normal	20	89	69	183	(17.5, 3.9) 80	(21.2, 3.7) 86	(20.3, 3.8) 87
T. C.	71	Both	Normal	40	67	33	163	(31.3, 3.0) 74	(46.9, 3.4) 77	(47.4, 3.4) 68
N. B. G.	72	Both	Tritan	36	92	84	161	(16.3, 2.6) 65	(19.5, 1.9) 111	(20.5, 2.2) 125
E. G. H.	72	Both	Tetartan	48	94	120	181	(43.4, 2.5) 79	(34.6, 1.5) 94	(42.3, 1.5) 74

Table 42.2 Test results for diabetic subjects

ID	Age	Sex	Eye	VA	Lanthony	FMH100	Trivector test			Ellipses test		
							P	D	T	F1	F2	F3
T. P. S.	42	F	RE	1	Normal	172	70	56	118	(67.3, 27) 94.1	(62.9, 47.7) 53.4	(73.8, 53.5) 101.4
			LE	1	Tritan	152	100	110	140	(23.3, 17.6) 69.5	(37.9, 22.4) 78.3	(46.6, 25.1) 89.8
C. C.	60	F	RE	1	—	88	88	101	127	(39.9, 19.2) 88.1	(43.1, 20.2) 87.0	(29.8, 19.9) 64.1
			LE	1	—	108	108	161	179	(25.5, 16.2) 80.8	(38.2, 14.8) 90.8	(36.8, 23.8) 53.4
S. K.	60	M	RE	1	Tritan difuse	128	128	107	101	(27.7, 7.9) 80.8	(36, 11.1) 94.0	(28.6, 9.8) 90.8
			LE	1	Tritan	140	140	72	46	(38.9, 13.6) 88.7	(45.2, 17.5) 97.0	(39.7, 23.6) 82.0
I. A. M.	61	M	RE	1	Undefined	312	132	144	84	(193.5, 2.1) 78.6	(128.8, 2.4) 77.1	(96.4, 2.4) 87.9
			LE	1	Deutan	132	312	144	128	(115.5, 2.4) 84.6	(81.1, 2.5) 91.8	(108.4, 2.0) 78.0
P. B. A.	63	M	RE	0,9	—	116	124	164	193	(58.2, 22.3) 78.8	(35.6, 20.0) 94.6	(42.1, 22.8) 62.5
			LE	0,7	—	140	105	166	369	(44, 17.4) 94.7	(46.3, 16.4) 107.9	(39.1, 19.2) 75.0
A. K. S.	67	F	RE	0,9	Normal	8	—	—	—	(33.9, 1.1) 86.1	(36.8, 1.2) 95.4	(46.6, 1.5) 80.3
			LE	0,9	Normal	0	42	46	153	(154.3, 1.1) 80.1	(39.4, 1.4) 81.8	(55.9, 1.0) 85.2
J. M. P	43	M	RE	1	—	—	81	65	86	(17.0, 9.0) 102.1	(20.8, 13.0) 124.8	(24.5, 9.3) 95.0
			LE	1	—	—	84	90	111	(15.0, 11.0) 104.6	(16.1, 12.5) 72.8	(23.5, 9.7) 103.3
J. L. F.	70	M	RE	1	Undefined	—	119	102	154	(58, 22.4) 79.4	(50, 28.1) 90.8	(79.5, 23.9) 91.0
			LE	1	Undefined	—	86	86	126	(32.4, 18.4) 81.2	(47.8, 25.3) 85.5	(42.8, 18.9) 97.6
N. L.	76	M	RE	0,9	Normal	80	97	73	294	(110.3, 15.4) 84.1	(75.7, 19.8) 88.0	(83.2, 25.6) 76.0
			LE	0,9	Normal	100	143	245	528	(69, 13.1) 88.5	(56.5, 19.9) 89.7	(76.5, 27.1) 72.2

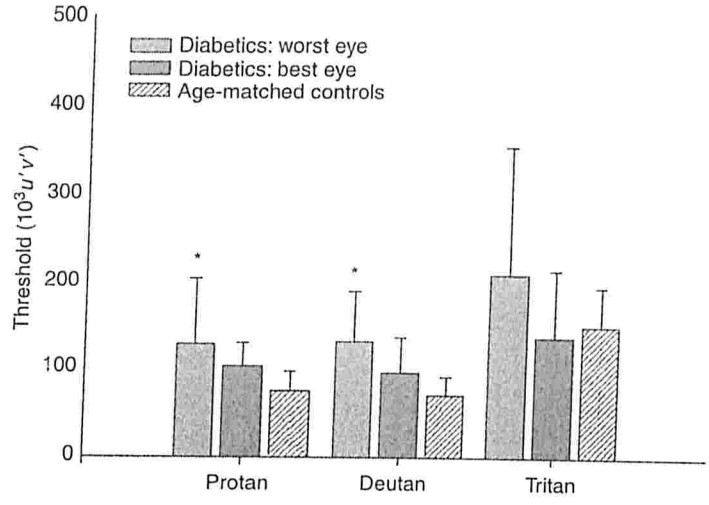

Figure 42.1 Results from the Trivector test showing thresholds in CIE 1976 $10^3 u'v'$ units obtained along the protan, deutan, and tritan axes for best and worst eyes of diabetic patients and age-matched controls. Asterisks indicate significant differences from the control data.

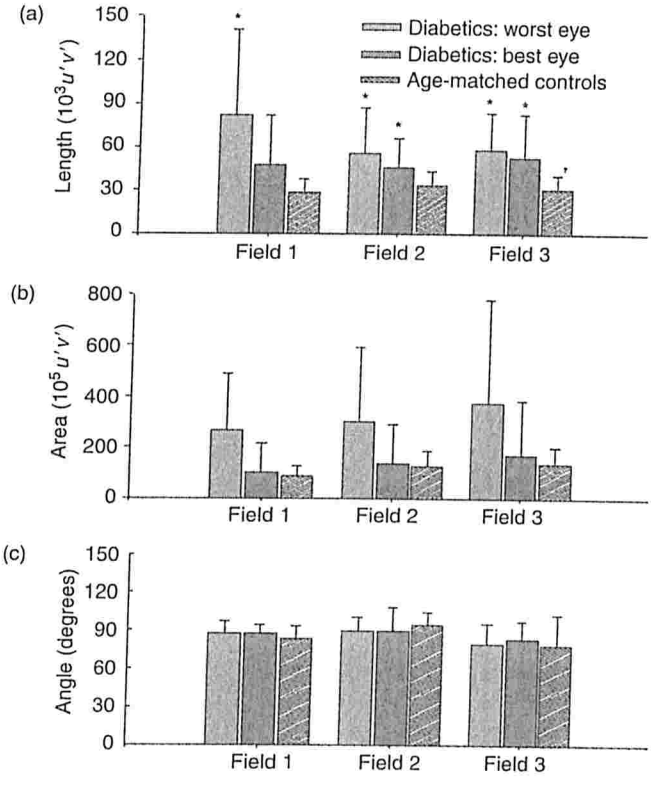

Figure 42.2 Average and standard deviations of CCT ellipse parameters of diabetic patients and age-matched controls. (a) Ellipse length; (b) Ellipse area; (c) Angle of major axis. Asterisks indicate significant differences from the control data.

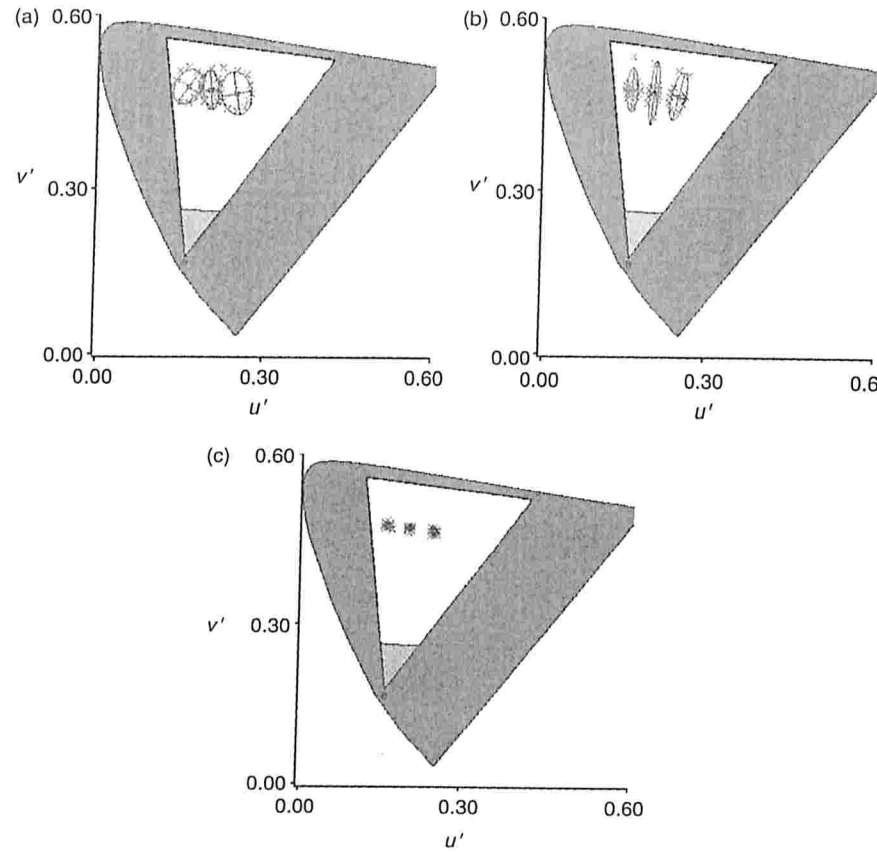

Figure 42.3 Test results showing thresholds and fitted ellipses plotted in the CIE 1976 $u'v'$ chromaticity diagram for: (a) diabetic patient with a diffuse loss; (b) diabetic patient with a tritan loss; (c) normal subject.

Patients were apparently classifiable into two groups: those with clear tritanopic losses and those with diffuse losses (Fig. 42.3).

Duration of DM II

The duration of diabetes was not correlated with the discrimination loss measured by the Trivector test nor with length or area of the CCT ellipses.

Comparison with other tests

The error score in the FM100 hue test was not predictive of CCT loss and showed unspecific losses in 13/16 eyes, a tritan loss in one eye and normal results in 2/16 eyes. The FM score was below 120 for 7/16 eyes, all of which showed losses in the CCT. One of the nine patients was not tested in the FM100.

The diagnosis made with the D15 and with the Lanthony tests coincided with the CCT in only 2/18 cases. Relative to the CCT results, the two tests underestimated losses in 30 per cent of the cases (5/18 eyes in the Lanthony and 6/18 in the D15) or produced a different diagnosis (5/18 eyes in the Lanthony and 4/18 eyes in the D15). The Lanthony desaturated test scores (Bowman 1982) were positively correlated with the protan and deutan axes in the Trivector test, although the correlation was not significant. Comparisons between the CCT and the Lanthony and D15 tests were possible in six patients; measurements were not made in the other three.

Discussion

The finding of colour vision loss in diabetic patients with no retinopathy is consistent with previous reports. Significant lengthening of implicit time and amplitude reduction were detected in the focal electroretinograms of non-retinopathic diabetic patients compared to control subjects (Deschenes *et al.* 1997). Non-retinopathic diabetic patients also had reduced visual acuity and contrast sensitivity and also colour vision loss, compared to normals (Deschenes *et al.* 1997; Ismail *et al.* 1998; Kurtenbach *et al.* 2000; North *et al.* 1997*a*). However, these functions did not distinguish between diabetics without diabetic retinopathy and those in the early stages of retinopathy.

In the present work we found that with one exception, all patients examined with the CCT had some degree of colour vision loss. Although a larger sample would be needed for a stronger claim, it seems that the CCT might be a more sensitive test than the instruments used previously. In fact, in several eyes (5/18) in which FM 100 test scores were relatively low (below 120) for 7/18 the CCT results showed either tritan or diffuse losses. The same happened with the Lanthony and the D15 tests. Of all the comparisons, the best agreement was between the CCT and the Lanthony scores.

The early clinical signs of diabetic retinopathy are mainly related to microvasculopathy represented by microaneurisms. These abnormalities develop after thickening of the capillary basement membrane and pericyte dropout. Since colour vision and other psychophysiological functions seem to be compromised even though clinical signs of diabetic retinopathy were not noticed, a neuropathy may be present. Aldose reductase is found in high concentration in retinal pericyte and Schwann cells and some investigators suggest that diabetic retinopathy and neuropathy may be caused by aldose reductase mediated damage.

We conclude that the CCT has full clinical testability and was the most sensitive of the tests used to detect colour vision loss. It is also evident from the present results that vision should be evaluated in diabetic patients from the earliest stages of the disease. Even though the duration of diabetes was not correlated with the extent of loss in the ellipses data, it was positively correlated with the tritan Trivector results.

Acknowledgements

This work was supported by FAPESP# 99/03013-7, FINEP #66.95.0407.00, CNPq #523303/95-5 and #521640/96-2 grants. Authors D. F. V. and J. M. S. are CNPq

research fellows. M. F. C. has a graduate fellowship from CAPES, whilst D. B. O. and M. G. have undergraduate fellowships from CNPq. We thank Claudiel Luiz dos Santos for administrative assistance.

References

Bownan, K. J. (1982). A method for quantitative scoring of the Farnsworth panel D-15. *Acta Ophthalmol. 60*(6), 907–16.

Deschenes, M. C., Coupland, S. G., Ross, S. A., & Fick, G. H. (1997). Early macular dysfunction detected by focal electroretinographic recording in non-insulin-dependent diabetics without retinopathy. *Documenta Ophthalmologica, 94*(3), 223–7.

Fristrom, B. (1998). Peripheral and central colour contrast sensitivity in diabetes. *Acta Ophthalmologica Scandinavica, 76*(5), 541–5.

Ismail, G. M., & Whitaker, D. (1998). Early detection of changes in visual function in diabetes mellitus. *Ophthalmic and Physiological Optics, 18*(1), 3–12.

Kurtenbach, A., Langrova, H., & Zrenner, E. (2000). Multifocal oscillatory potentials in type 1 diabetes without retinopathy. *Investigative Ophthalmology & Visual Science, 41*(10), 3234–41.

Lieth, E., Gardner, T. W., Barber, A. J., & Antonetti, D. A. (2000). Retinal neurodegeneration: early pathology in diabetes. *Clinical and Experimental Ophthalmology, 28*(1), 3–8.

MacAdam, D. L. (1942). Visual sensitivities to color differences in daylight. *Journal of the Optical Society of America, 32*, 247–74.

Mollon, J. D., & Reffin, J. P. (1989). A computer-controlled colour-vision test that combines the principles of Chibret and of Stilling. *Journal of Physiology—London, 414*, 5.

Mollon, J. D., & Reffin, J. P. (2000). *Handbook of the Cambridge Colour Test.* London, UK: Cambridge Research Systems.

North, R. V., Cooney, O., Chambers, D., Dolben, J., & Owens, D. R. (1997*a*). Does hyperglycaemia have an influence upon colour vision of patients with diabetes mellitus? *Ophthalmic Physiological Optics, 17*(2), 95–101.

North, R. V., Farrell, U., Banford, D., Jones, C., Gregory, J. W., Butler, G., & Owens, D. R. (1997*b*). Visual function in young IDDM patients over 8 years of age—A 4-year longitudinal study. *Diabetes Care, 20*(11), 1724–30.

Regan, B. C., Freudlander, N., Kolle, R., Mollon, J. D., & Paulus, W. (1998). Colour discrimination thresholds in Parkinson's disease: results obtained with a rapid computer-controlled colour vision test. *Vision Research, 38*, 3427–31.

Regan, B. C., Reffin, J. P., & Mollon, J. D. (1994). Luminance Noise and the Rapid-Determination of Discrimination Ellipses in Color Deficiency. *Vision Research, 34*(10), 1279–99.

Remky, A., Arend, O., & Hendricks, S. (2000). Short-wavelength automated perimetry and capillary density in early diabetic maculopathy. *Investigative Ophthalmology & Visual Science, 41*(1), 274–81.

Tregear, S. J., Knowles, P. J., Ripley, L. G., & Casswell, A. G. (1997). Chromatic-contrast threshold impairment in diabetes. *Eye, 11*, 537–46.

Tregear, S. J., Ripley, L. G., Knowles, P. J., Gilday, R. T., Dealwis, D. V., & Reffin, J. P. (1994). Automated tritan discrimination sensitivity—a new clinical technique for the effective screening of severe diabetic-retinopathy. *International Journal of Psychophysiology, 16*(2–3), 191–8.

NORMAL AND DEFECTIVE COLOUR VISION

Edited by

J. D. MOLLON

University of Cambridge

J. POKORNY

University of Chicago

and

K. KNOBLAUCH

University of Lyon

OXFORD

UNIVERSITY PRESS

MOT USP

OXFORD
UNIVERSITY PRESS
Great Clarendon Street, Oxford OX2 6DP

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide in

Oxford New York

Auckland Bangkok Buenos Aires Cape Town Chennai
Dar es Salaam Delhi Hong Kong Istanbul Karachi Kolkata
Kuala Lumpur Madrid Melbourne Mexico City Mumbai Nairobi
São Paulo Shanghai Taipei Tokyo Toronto

Oxford is a registered trade mark of Oxford University Press
in the UK and in certain other countries

Published in the United States
by Oxford University Press Inc., New York

© Oxford University Press, 2003

The moral rights of the authors have been asserted

Database right Oxford University Press (maker)

First published 2003

All rights reserved. No part of this publication may be reproduced,
stored in a retrieval system, or transmitted, in any form or by any means,
without the prior permission in writing of Oxford University Press,
or as expressly permitted by law, or under terms agreed with the appropriate
reprographics rights organization. Enquiries concerning reproduction
outside the scope of the above should be sent to the Rights Department,
Oxford University Press, at the address above

You must not circulate this book in any other binding or cover
and you must impose this same condition on any acquirer

British Library Cataloging in Publication Data
(Data available)

Library of Congress Cataloging in Publication Data
(Data available)

ISBN 0 19 852530 3

10 9 8 7 6 5 4 3 2 1

Typeset by Newgen Imaging Systems (P) Ltd., Chennai, India
Printed in Great Britain
on acid-free paper by
Biddles Ltd, Guildford and King's Lynn