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Human cataract formation

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Symposium on Human Cataract Formation, held at the Ciba Foundation, London, 25–27 October 1983

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Introduction

A. SPECTOR

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It is ten years since the first Ciba Foundation symposium on the human lens and cataract (Ciba Foundation 1973). At that time, little work had been done on the human lens. Most studies had utilized bovine, rat and rabbit material. General aspects of metabolism, protein chemistry and morphology had been delineated. An understanding of diabetic cataract was emerging, and some concepts had been cautiously advanced to explain aspects of cataract development.

The Ciba Foundation symposium in 1973 changed the emphasis, changed the perception of the field. A number of laboratories turned to the direct study of the human lens and human cataract. Some scientists who had studied the animal lens for a considerable period now began to investigate the human lens for the first time. Stimulated by the Ciba Foundation meeting and the discussions on the classification of cataract, American cataract researchers joined together to collaborate on the study of human lenses. A system of classifying human lenses was developed by Dr Leo Chylack under this programme, and an effective computer network for analysing, storing and sharing data was developed. Cooperative programmes also emerged in Japan and in Europe, to some extent stimulated and encouraged by the experience of the American Cooperative Cataract Research Group.

The success of the CCRG classification system has led to the tendency to relate the type of opacity to the initiating cause. It should be remembered, however, that opacification is the final step in cataract formation. For example, in animal models of sugar-induced cataract, the sudden opacification of the inner region of the lens is far removed from the initiating site. Caution must be exercised in presuming that an opaque region of the tissue can reveal the initiating events that have led to its present status, or even suggest where in the lens, or elsewhere in the organism, the process began.

Considerable progress has been made in the past ten years. It has also become evident that a simple extrapolation of the animal data to the human lens is not possible. There are a number of reasons for this. Long-term ageing changes have been found which had not been anticipated from studies with

relatively short-lived mammals. Aspects of human lens biology, such as growth, hydration, relative enzyme concentrations and changes in protein structure, are found to be different. Furthermore, we have been confronted with a diversity of cataracts, at least in terms of their morphological features.

We are now at another cross-roads. New surgical procedures for extracting cataracts, which result in the destruction of the tissue, are becoming popular. This development lends an urgency to the need to discover and improve non-invasive techniques for studying the lens in the human as well as in animal models. Recently, light-scattering techniques have been refined and applied at both the molecular and cellular levels. New techniques, such as nuclear magnetic resonance and fluorescence spectroscopy, are gradually emerging as powerful non-invasive analytical tools. We shall become increasingly dependent on such techniques, and also on areas of the world where intracapsular cataract extraction remains popular. The non-invasive methods will also have a central role in confirming the observations obtained in the test-tube and in culture systems with intact lenses or with epithelial cell preparations. They should provide important insights into the effectiveness of new drugs in retarding or preventing cataracts.

There is another aspect to the present cross-roads confronting lens researchers. A sufficient body of information is becoming available for a critical evaluation to be made of mechanisms in the development of cataract. Indeed, while solutions elude us, hypotheses abound. There now are a host of concepts to explain cataract, including osmotic imbalance related to the accumulation of sugar alcohols via aldose reductase; oxidative insult; the development of high molecular weight protein aggregates and the phase separation of protein components in the cytoplasm; calcium imbalance; genetic defects; alterations in the cytoskeleton; insufficiency of glucose causing metabolic imbalance and instability of certain enzymes; subliminal factors associated with ageing, diet, and drug intake; and many others. It is time to begin an evaluation of these concepts with the information now available, and to question their validity. It is probable that some of them are related and are part of a general route of opacification. It is important to design experiments and model systems for the purpose of testing our concepts of cataract formation, to allow us to reject or strengthen our present ideas.

We shall consider some of these problems at this meeting. If we are successful, perhaps this symposium will give a new direction to cataract research as did its predecessor, a decade ago.

REFERENCE

Ciba Foundation 1973 The human lens—in relation to cataract. Associated Scientific Publishers, Amsterdam (Ciba Found Symp 19)

Classification of human cataractous change by the American Cooperative Cataract Research Group method

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Abstract. The American Cooperative Cataract Research Group (CCRG) has adopted a system of classifying cataractous changes in excised human cataracts that is based on separate and independent photographic documentation of opacification and nuclear colour. The classification data can be simplified according to the needs of the scientist in his or her effort to measure clinically or scientifically significant associations between laboratory measures and cataractous change. The association between nuclear colour and the extent of cortical opacification and the intensity of nuclear opacification has been studied and found to be insignificant. These results justify the recommendation that nuclear colour be abandoned as the single index of severity of any type of senile cataractous change.

The adaptability of this system to *in vivo* use in epidemiological and other studies of the natural history of cataractous change is discussed. Its limitations are outlined. The system may offer a basis for international cooperation in cataract classification.

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In 1976, at the annual meeting of the Association for Research in Vision and Ophthalmology in the US, an informal meeting of lens scientists discussed the feasibility of increasing the emphasis on human, as opposed to animal, cataract research. There was considerable enthusiasm for this idea, and shortly thereafter the Cooperative Cararact Research Group (CCRG) was formed. In 1980, funding as a consortium of 23 laboratories was obtained from the National Eye Institute. Initially the major objectives of the consortium were:(1) to increase the supply of human cataracts available to the lens scientist, so that studies of biochemistry, physiology, anatomy and so on could proceed in parallel with animal experimentation under way in the laboratory; (2) to develop a sound method of classifying cataractous changes in the human lens; and (3) to develop a method of exchanging information among CCRG scientists. In the

initial grant application, a section on *in vivo* studies was included but was later removed, because it was judged to be premature. The system of cataract classification is presented in this symposium in its present state of development, but it is undergoing continuous improvement. It is appropriate that the system be discussed here, since the symposium aims to evaluate critically various hypotheses of cataract formation; the CCRG classification system may provide an infrastructure for just such an evaluation. I shall discuss the suitability of this system for use *in vivo* and mention alternative or supplementary non-invasive techniques for gaining information about the mechanisms of cataract formation. I hope to convince you that the CCRG classification system is scientifically sound, and to persuade you to adopt it as the system of classification of cataracts in laboratories in Europe as well as in the US.

Background

For decades clinicians have described cataractous changes with a series of internationally understood and accepted terms (subcapsular, anterior, equatorial and posterior cortical, supranuclear and nuclear opacification). Other terms implying aetiological significance (such as radiation cataract, steroid cataract, or traumatic cataract) have been used, but I do not regard this clinical effort to be legitimate 'classification'. I have chosen to define classification as the description and organized grouping of the discrete features of lens opacities. The clinician derives no significant benefit from the rigorous application of an 'organized' system of terminology. In response to the unsuitability of the clinical terminology, Pirie (1968) suggested organizing insoluble lens proteins according to the intensity of colour (from yellow to black) of the nuclei from which the protein was derived. Others (Duncan & Bushell 1979, Marcantonio et al 1980, Duncan 1981) have proposed similar or somewhat amplified classification systems. Each of these systems uses either observation or photography of the cataract against a white background and assumes that the intensity of nuclear colour, on a spectrum of pale yellow through to yellow-brown and black, is a measure of the *severity* of cataract formation. None of these scientists has experimentally tested the validity of this assumption. Other weaknesses in some of the European proposals for cataract classification are the use of cataracts which have been frozen or stored in salt solution. We suspected that such treatment would obscure or at least drastically alter the appearance of the cataract.

In planning the design of the CCRG classification system, I stressed the importance of:

(1) Photographing cataracts against a black background with white fluor-

escent light. We found these cataractous changes to be invisible when the lens was viewed against a white background.

(2) Obtaining a separate photograph of the lens against a white background, so as to estimate nuclear colour.

(3) Photographing the lens immediately after extraction from the globe; to facilitate this, the technicians and the photographic apparatus were present in the operating rooms of the Massachusetts Eye and Ear Infirmary.

(4) Describing semi-quantitatively the extent of subcapsular, cortical and supranuclear opacification with measurable variables, and the relative intensity of nuclear opacification and colour with ranked or ordinal variables.

(5) Creating a permanent set of stereoscopic 35 mm colour transparencies of cataracts that can be used in classifying cataracts and can be recalled and reviewed if revision of the system of classification is indicated.

(6) Facilitating the simplification of the raw classification data.

The system has been described at each stage of its evaluation (Chylack 1978, Chylack et al 1983, 1984b). The chosen terminology puts all cataracts into one of three groups, as follows:

Hypermature (H): a totally opaque lens that has undergone marked swelling in the antero-posterior dimension.

Mature (M): a totally opaque lens in which no recognizable normal anatomical zone remains, but in which there is no appreciable antero-posterior swelling.

Immature (I): an opacity which does not totally obscure all normal anatomical regions of the lens.

All immature cataracts (I) possess some amount of normal lens anatomy, and the cataractous changes are grouped into the following zones (see Fig. 1): CXA (anterior cortex), CXE (equatorial cortex), CXP (posterior cortex), SCA (subcapsular anterior), SCP (subcapsular posterior), SN (supranuclear)

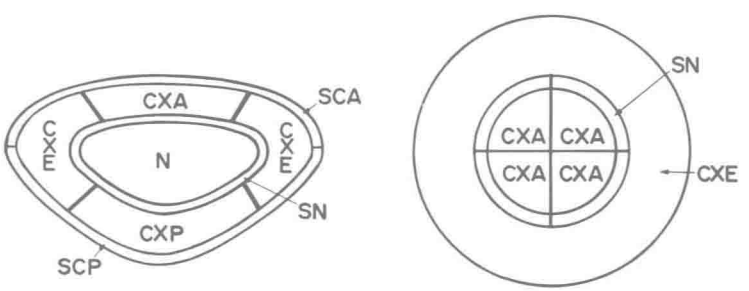

FIG. 1. Diagram of the principal anatomical zones of the human lens as used in the CCRG classification scheme. SCA, SCP: subcapsular, anterior and posterior respectively; CXA, CXE, CXP: anterior, equatorial and posterior cortical zones respectively; SN: supranuclear; N: nuclear. Left view: sagittal; right view: frontal with anterior surface up.

and N (nuclear). Nuclear colour is designated by NS (nuclear sclerosis). Subcapsular opacification is graded by relating the opaque zone to a series of concentric circles (Fig. 2). The outer circle represents the equatorial circle of the lens. CXA, CXE, CXP and SN opacifications are graded by the cumulative extent of quadrantic involvement (subscripts 1–4) occupied by the opacity. Nuclear cataract (N) is graded by the density, as judged by the degree (1–4) to which a slit-beam image passing through the lens is obscured. NS is graded by the colour on an eight-step spectrum from clear to very pale yellow, pale

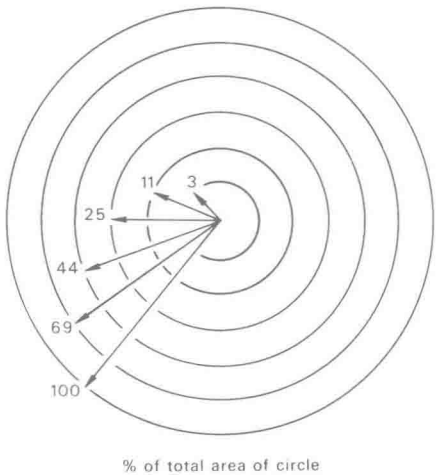

FIG. 2. An aid to the estimation of the area involved in a subcapsular cataract. A set of concentric circles, the largest of which represents the equatorial circle of the lens. The smaller circles are designated with a number representing the percentage of the area of the equatorial circle occupied by the designated circle. The classifier uses these circles to estimate the approximate size of an SCA or SCP opacity in a human lens.

yellow, yellow, dark yellow, very dark yellow, brown and black. The classifier uses six stereoscopic views of the lens and records the classification on cards containing identification information and clinical data as well as the classification codes. A raw classification might appear, simply, as 'M', or be as complex as 'I SCA_3 CXA_2 N_4 NS_4' or 'I SN_3 CXE_2 CXP_2 N_1 NS_8'.

'M' is a totally opaque lens in which the colour of the nucleus cannot be graded accurately because of the light scattering properties of the perinuclear cortex.

'I SCA_3 CXA_2 N_4 NS_4' is an immature cataract in which normal and opacified zones are seen. The 'SCA_3' term indicates that the approximate area of the anterior subcapsular opacity is 3% of the area of the equatorial circle of the lens (Fig. 2). The 'CXA_2' term indicates that approximately two quadrants, or 50%

of the anterior cortex (Fig. 1), is occupied by opacity. The opacity need not be exactly quadrantic in shape but should occupy 50% of the CXA zone. The 'N_4' term describes a nuclear opacity through which a slit beam cannot pass. This is evident in a slit-view of the cataract against a black background in which the beam does not reach and, therefore, cannot be reflected from the black surface underlying the lens. The 'NS_4' term indicates that the colour of the nucleus against a white background is yellow.

The '$I\,SN_3\,CXE_2\,CXP_2\,N_1\,NS_8$' classification denotes an immature cataract in which three quadrants of the supranuclear zone 'SN_3' are opaque. If the SN zones contain clear and opaque regions, the cumulative extent of the opacity is used. Likewise 'CXE_2' and 'CXP_2' indicate two quadrants-worth of equatorial and posterior cortical opacity respectively. The 'N_1' term describes a faint nuclear opacity, one in which a slit beam passes through the nucleus to the black surface beneath the lens and appears slightly blurred. If the blur was moderate, the term would be 'N_2'; if the blur was marked, but not total, the term would be 'N_3'. The 'NS_8' term indicates the colour of the nucleus to be black or blackish brown against a white background.

When the CCRG Consortium began functioning, I was the only classifier; all lens photos were sent to me, classified and returned to the scientist of origin. I made an attempt to test the consistency with which I was classifying lenses. A subset of 82 lenses, representing the same proportion of simple and compound cataracts as in the total population, was classified by me on two occasions, 48 hours apart. The sequence of cataracts was changed at the second effort, and the results of the first effort were not available the second time. The two sets of classification data were compared and errors analysed. The results (Chylack et al 1983) demonstrated a high degree of consistency in my classification, with the following exceptions:

(1) It was difficult to distinguish consistently between anterior subcapsular opacities (SCA) and anterior cortical opacities (CXA), and between the posterior subcapsular and posterior cortical opacities (SCP and CXP). Since this distinction is likely not to be important, it was not regarded as a major weakness.

(2) When nuclear colour (NS) was estimated, there were 20/73 cases in which the NS subscript differed by one grade; 9/82 lenses were H or M, and in these, NS cannot be classified accurately. In no case did the estimate of NS differ by more than one grade. In using the data on nuclear colour it therefore seemed best to condense the eight steps in the NS index to four.

With increased acceptance of the CCRG classification system it became possible to test the ability of other scientists to classify cataractous change consistently. With the help of Dr Bernard Rosner, a protocol was developed in which three examiners from outside Boston came to Boston for two days of intensive instruction in the technique of classification. Each examiner classified