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Quantitative studies in stereochronoscopy (Sc): application to the disc in glaucoma

I. Phenomenology

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Abstract. In some details our standard procedure of stereochronoscopic disc picture-taking has been improved. For clinical use (demonstration of a change in the disc surface) a semi-quantitative evaluation with a stereoscope is generally sufficient. For a more accurate and quantitative analysis a flicker comparator is used. A graphical or numerical display of the results allows the follow-up of changes at a given location on the disc over any time interval, e.g. several years in glaucoma simplex, if pictures are taken every 2–4 months. Characteristic curve courses result, of which we describe (1) to and fro movement of the position of a given object on the disc, "papillary unrest" (2) progression of parallax, and (3) "events". The difficulty of judging the efficacy of a therapy is made evident. Here stereochronoscopy should prove to be useful when employed in the form of control charts.

Introduction

Recently the pendulum of opinion regarding the problem of the genesis of chronic glaucoma has begun to swing the other way. There is doubt as to whether increased intraocular pressure (IOP), at least on its own, is the cause of the glaucomatous decay of function. However, we have shown on previous occasions [4] that the result of measurement of eye pressure, even the best measurement and even if the increased pressure is the cause of the decay of visual function, is not a usable measure of the damage. For there is not only *one* eye pressure in a patient, and how the temporal succession of different pressures affects the function is not known. In this context the work of Niesel and Flammer [12] should be mentioned. Thus the devaluation of the importance of IOP can be understood. Previously all high-pressure values of small statistical probability were equated with damage pressure. Later an essential distinction was made between ocular hypertension (IOP which seems suspicious but is not accompanied by visual field defects) and beginning glaucoma with changes in the visual field and/or with glaucomatous excavation, with or without increased IOP, whatever "increased" may mean. In many cases of established glaucoma Drance [3] recently found striate haemorrhages in the disc, not always with corresponding field defects. These haemorrhages were declared by Krakau [9] to be the basic and early symptom of chronic glaucoma; he reduced IOP to the status of a minor concomitant symptom. However, we have known for a long time that the so-called "central venous thrombosis", or "thrombosis of branches of the retinal vein" (i.e. more or less extended striate haemorrhages of the fundus in cases of restriction of venous circulation, and not only in cases of real thrombotic blockage) is very frequent in cases of chronic glaucoma and has been taken to be a sign of circulatory embarrassment *caused* by glaucoma. What happens in the retina in advanced cases of glaucoma may also occur in the disc at any stage of the disease, and the explanation of both phenomena could be the same.

The different hypotheses regarding the genesis of glaucoma affect, not always in a favourable way, the evaluation of the efficiency of a therapy (e.g. β-blockers). First of all, we do not know how long we have to wait to judge the efficiency of a medication. We do not know how long it takes before diurnal or weekly peaks of IOP begin to nibble unequivocally at the visual field. Neither do we know how long we must wait to be sure that during our observation period a sufficient number of rare single occurrences has arisen (e.g. haemorrhages) to appear as visual field defects, or what sort of therapy we should apply. The conclusion must be that we know too little. Therefore we welcome every hypothesis that can be refuted, in order to increase our reserve of experience. Also we welcome any method which can indicate measurable progressive changes in glaucoma cases, independently of increased IOP or of haemorrhages. Such a method is the following up of the visual field; a second one is Sc. Both are non-specific for glaucoma simplex. The first has been well examined and has reached a peak of accuracy in automatic perimetry which could hardly be improved upon. Results from the second method are still rare. In the following we will investigate it phenomenologically and attempt to standardize it.

In earlier papers [5–8, 10] we have described the conditions necessary for rapid detection of small changes in the surface configuration of the disc. The principle is that a displacement with time of an object will manifest itself on successive pictures as an apparent spatial effect, either by handling the pictures as stereoscopic pairs (any displacement then results in a three-dimensional effect), or by showing a parallactic jump when two pictures are presented alternately within the same frame. The first method is simple

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but presupposes a good stereoscopic faculty of the observer. Moreover it is semi-quantitative, at best, in the form in which we apply it. The second method, flicker comparison, was developed by Pulfrich [13]. It lends itself well to quantitative evaluation. Bengtsson and Krakau [2] were the first to apply it to the fundus.

We shall summarize here our procedure of picture-taking and evaluation which has evolved on the basis of a considerable amount of material (more than 600 patients, most of them seen several times). The procedure is tailored to glaucoma simplex cases in order to obtain the answers to some of the questions we have briefly discussed above. If application of Sc to other diseases is planned, some minor modifications should be made.

Methods

Photography

The technical conditions to be observed in taking fundus pictures intended for Sc use (exact centering of the camera axis on the patient's cornea and approximate centering of the object within the frame) have been described extensively in earlier papers [5,6, 10]. Some additional remarks are:

1) Besides black-and-white pictures it is also desirable to take colour pictures or to use filters, since small haemorrhages on the disc show up much better.

2) In the case of chronic glaucoma it is advisable to take a series of at least 3–4 good pictures every 3 months in order to create a basis for the determination of the standard error of the method.

3) Bengtsson and Krakau [1] have proposed focusing the fundus camera on the disc, not by direct observation of the image, but by using the refraction of the eye in question for positioning the camera extension accordingly. We have found that this method may indeed have advantages in cases of turbidity of the media, insufficient mydriasis, or when the operator experiences difficulty with his accommodation. Note, however, that refraction of the macula and the disc is not necessarily the same.

4) Artifacts generated by the arterial pulse, and to some extent also by the venous pulse, can be avoided by synchronization of exposure with the R peak of the ECG. We have somewhat simplified this method by connecting two of the electrodes to insulated metal handles on the chin-rest support which the patient grips with his hands via saline-moistened blotting paper. The third electrode is connected to the camera stand. The ECG is then distorted but in most cases the R peak still stands out sufficiently to trigger the camera via a relay. A time delay adaptable to pulse frequency is provided. As much artifact as is caused by the venous pulse irregularity [7] must be included in the measuring error. It is therefore recommended that more than three pictures are taken of each eye in a session.

5) In a recent paper [11] it has been shown that in cases of high ametropia the distance between the camera and the patient's eye must be held constant with great care, since magnification is more dependent on this distance the greater the ametropia. Whereas a difference in image size of a few percent hardly affects the evaluation of a stereo pair, measurements with the flicker comparator are very sensitive to this. Even when the possibility of compensating for such "aniseikonia" is provided in the instrument (as is the case in ours), an uncertainty remains when the true amount of the difference is not known. In such cases it is therefore imperative to use the lateral corneal reflexes to adjust the distance carefully, as described in [10].

6) Whereas the Sc method is highly sensitive to changes of an object in two dimensions, it provides no clue whatsoever about its real three-dimensional variation. If information is also required – justifiably – with regard to the latter, conventional stereo pictures must be taken from time to time, for example, once or twice a year in the case of glaucoma simplex. With our equipment this is particularly simple and can be done without the use of an Allen separator. Indeed it is sufficient to take two pictures not by using the central corneal reflex to adjust the camera axis on the cross hairs, but first one and then the other of the two reflexes generated by the lateral auxiliary lenses that appear on both sides of the central reflex. At low ametropia the resulting stereo pair then corresponds to a stereo basis of 2.1 mm. For a thorough statistical analysis of a glaucoma case at least 8–10 picture series are required.

This therefore requires about 2 years of follow-up. (Conversely, in the case of a choked disc this period will be only a few weeks.) We now dispose of the necessary material to do all the calculations desired.

Evaluation

Semi-quantitatively with a stereoscope. This is our original method as described in [5]. It was later modified into what we call the "card system" (or register) [10] where magnified copies are glued on cards in a prealigned manner so that all pictures of an eye can rapidly be compared inter se in two azimuths at right angles. Thus, it is possible to decide whether a perceived change has taken place preponderantly in a horizontal or vertical direction, or at an azimuth of $\pm 45°$. In principle our earlier method of mounting the pictures on two synchronously rotatable discs [6] allowed the determination of the azimuth of the direction of maximum change with higher accuracy, but it is rather time-consuming and the increase in information is often not worthwhile. For the great majority of our glaucoma patients we have used this card system for follow-up. It provides reliable information about whether disc changes are present, if they are slow or rapid, progressive or perhaps of changing sign. In addition, this method is relatively insensitive to a moderate blur of the pictures, especially when only one of a pair is involved. It is also useful for a rapid preliminary examination before quantitative measurements with the flicker comparator are started.

Quantitative measurement. This is done directly on the film negatives with a flicker comparator as described in [10]. The temporal change of a given point is measured, that is, parallax. As many points as possible in the surroundings of the disc, which are not liable to have changed, are superimposed by adjusting operations on one or both films (the nasal rim of the disc and its neighbourhood are often a preferred area). Parallax is measured by a rotatable glass plate the angle of inclination of which is transformed into electrical voltage by connection of the axis to a potenti-

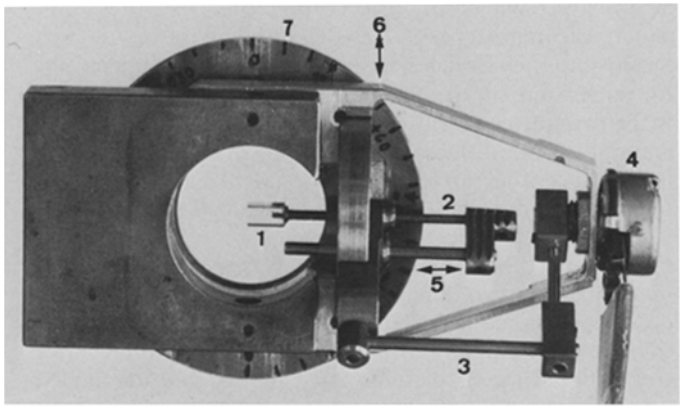


Fig. 1. Measuring device used with the flicker comparator (0.9 × natural size). (*1*) Small glass plate that can be tilted about axis (*2*). Its angle of rotation is transferred by rod (*3*) to the slide wire contact of potentiometer (*4*). By two slide movements (*5*) and (*6*) at right angles, plate (*1*) can be placed over every area of the film picture. The whole unit is rotated on its base to orient axis (*2*) perpendicularly to the direction of maximum change within the specific area of the picture examined, and its azimuth is read on scale (*7*)

Table 1. Data for cases (a)–(d) of Fig. 2

Case	Eye	Age at 1. session	Diagnosis	c/d
(a) D.B.	OD	30 yrs	Juvenile glaucoma	0.9
(b) T.S.	OS	24 yrs	Glaucoma suspect	0.5
(c) M.C.	OD	25 yrs	Secondary glaucoma with congenital cataract	0.3
(d) M.B.	OS	51 yrs	Glaucoma simplex	0.5

Table 2. Approximate correspondence between adopted qualitative scale for stereo effects and quantitative ranges found by flicker comparison on disc pictures at an overall magnification of 15 ×

Qualitative scale	Corresponding range (μm in fundus)
No effect	0– 4
Weak	4–15
Medium	15–35
Strong	>35

ometer. The scale of the voltmeter is calibrated directly in micrometers on the fundus, taking into account the non-linear relationship between inclination and image displacement of a plane-parallel glass plate. In contrast to the device of Bengtsson and Krakau [2] we used a plate of only 3 × 6 mm which is moved over to the place of interest on the film (Fig. 1). This enables the surroundings to remain observable for correct superimposition.

Besides the measurement of parallax it may be of interest to note also the azimuth of a change; this may be related to the course of the nerve fibres. Measurements with the flicker comparator are more sensitive to poor picture definition than simple stereoscopic observation. For an experienced observer the adjustment and parallax measurement at a single point of a given picture pair takes about 2 min, so that the time required for a curve similar to those of Fig. 2 is of the order of 40 min.

Remarks concerning nomenclature. We call the disc pictures taken at one and the same session a "series". Differences between pictures of the same series, caused for example by pulse or deficient centering, we call "photoparallaxes". A "series parallax" is the position difference of an object point between time 0 and time *t*. A plot of all such parallaxes versus time constitutes the "parallax – time diagram" of an object point in a given disc.

One should always compare every picture of one series with every one of the other series in order to detect the amount of photoparallaxes. These data are required when a statistical evaluation is intended (see below).

Results

The graphic display of the results obtained by the flicker comparator shows some phenomena that suggest further investigation: no parallax may show up for years; parallax may vary linearly or non-linearly, continually or discontinually; it may vary to and fro by anomalously high amounts with or without a mean slope at the same time.

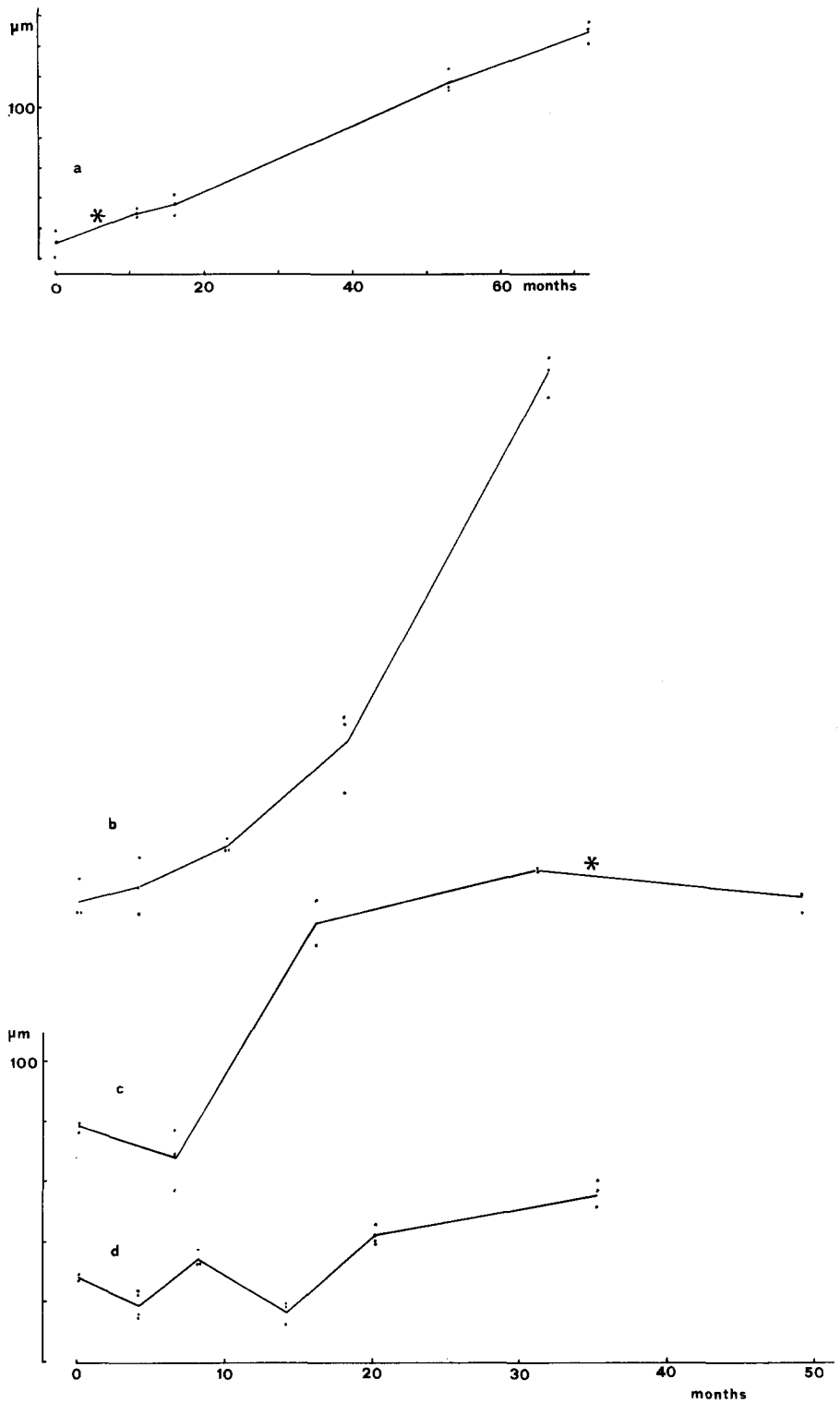
Some characteristic examples are shown in Fig. 2a–d. However, it must be understood that the majority of our curves could not unequivocally be attributed to one of these types but rather appeared to be some combination of them. Table 1 contains data for cases a–d. These and other phenomena, for example, a different course on different disc locations, can be further investigated by methods of modern statistics. One thing, however, stands out quite clearly: the phenomena mentioned are not especially useful for a *rapid* diagnosis of glaucoma. On the other hand, their follow-up appears to be appropriate for the surveillance of a suspected or treated glaucoma. For this purpose a procedure is proposed which has proved very useful in practical control of mass article production, the system of "control charts". We intend to discuss in another paper its merits in the survey of chronic glaucoma.

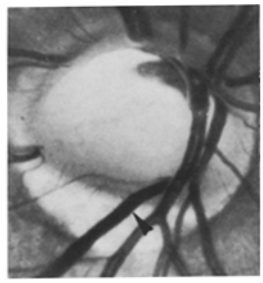
Further results of our investigations are as follows: For fairly good pictures the uncertainty of measurement (the measuring error) within a series corresponds to 5–10 μm in the fundus. Table 2 shows that the limit of stereoscopic discrimination for normal eyes is of the same order. The material for our quantitative study (82 eyes) was not uniform with respect to the temporal distribution of sessions (intervals of from 3 months up to 2 years over time spans from 1.5 to 4.5 years). We learned that roughly equal intervals would have been preferable (2–4 months in glaucoma simplex).

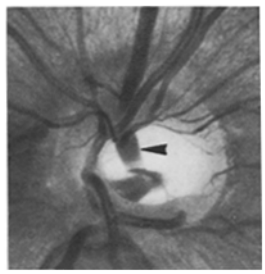
In 11 of 12 normal eyes over periods of 3–6 years we found a normal variation of the mean values and no temporal trend. One eye (Fig. 3) showed a slight linear displacement of a group of small vessels near the centre of the disc (18 μm over 5.5 years). We do not know why.

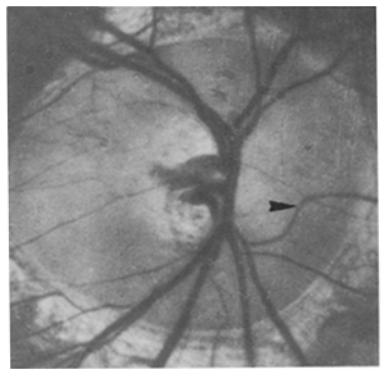
Before we proceed to the pathophysiological interpretation of the parameters obtained, three remarks may be in order:

1) As stated above, Sc results are not specific for glaucoma. In the diagnosis of glaucoma they are of value only in context with other findings.









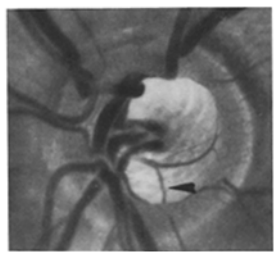


Fig. 2. Examples of parallax – time diagrams. *a*) linear increase, *b*) non-linear continuous course, *c*) non-linear discontinuous course, *d*) to-and-fro variation without a distinct slope. All the pictures from the second date onwards (in general three per session) were compared to one and the same picture taken on the first date. The results of measurement are given as points in the diagrams. The means of every date are connected by straight lines. Asterisks in diagrams *a*) and *c*) mark the dates of trabeculectomy. In the corresponding disc photographs the *arrows* point to the vessels that underwent displacement and indicate their direction and azimuth

2) As also mentioned the results of Sc are incomplete in the sense that of three-dimensional changes only those in the x-y plane are detected. Signs of + and − only mean directions of change within this plane. Note, however, that the results of visual field measurements are incomplete, too, since they equate threshold measurements with measurement of visual function in general.

3) We must remember that we presuppose a certain stability of an uninfluenced disc configuration. We have to ask how

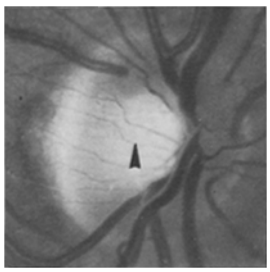


Fig. 3. Example of a normal eye showing slight displacement of small vessels near the disc centre (*arrow*)

far this is justified. We have seen a case with a heavy excavation (Fig. 2a), c/d ~ 0.9, where even years after successful glaucoma surgery, i.e. normal pressure and no change of the visual field, the phenomenon of fill-up within the disc continued; in this context see Shaffer and Hetherington [14]. We also saw a case of cortisone glaucoma with advanced visual field defects. The disc was pale but not excavated. Stopping local cortisone administration promptly normalized the tension. The visual field remained unchanged, but 2 years later the disc was found to be deeply excavated. These examples suggest that there is no close correlation between changes in the disc configuration and progression of field defects.

Pathophysiological interpretation

We should like to comment on the following three items: papillary unrest, progression, and discontinuities in the parallax – time diagrams. We speak of "papillary unrest" of an object on the disc when its parallax changes to and fro with time more than normally (Fig. 2d). "Progression" means that a parallax has increased with time.

1) "Papillary unrest" apparently means "influence upsetting the surface equilibrium followed by recovery" (e.g. by great variations of pressure). However, one must not forget that in Sc, changes in the third dimension cannot be seen. As mentioned above, only true stereo pairs obtained as described can provide the necessary information to avoid mistaking progression in depth for recovery in the x-y plane. Thus reversal of parallax does not necessarily mean recovery.

2) "Progression" over longer periods is "irreversible development" in most cases. This may vary at different locations of the disc.

3) A discontinuity signifies an event that has already happened and that has to be identified. Progression without a discontinuity may therefore also mean that a more or less linear progression has been preceded by an event that we have missed.

With the technique described, which is easily supported by the patient, some of the questions metioned will be examined.

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