N. Rietbrock · B. G. Woodcock
Editors

Color Vision in Clinical Pharmacology

The Proceedings
of the 3rd International Symposium
on Methods in Clinical Pharmacology
Frankfurt/Main

Norber[illegible] J. Woodcock (Eds.)

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The Editors

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Preface

This book contains the proceedings of the 3rd International Symposium on Methods in Clinical Pharmacology. The theme "Color Vision" is seldom met in Clinical Pharmacology but the retina offers a number of new possibilities as a pharmacological model and as an area for basic pharmacological research.

Clinical Pharmacology today focuses predominantly on drug monitoring. Pharmacokinetic principles have already been worked out for us but our mastery of pharmacodynamic problems is not so well advanced. There is for example an urgent need for new methods of assessing neural and sensory effects of drugs. This is one of the topics touched on by this Symposium. The Symposium also deals with recent clinical investigations on color vision impairment induced by drugs, with special reference to the cardiac glycosides.

The clinical pharmacologist in the past has given little attention to the mechanism by which drugs affect vision and few studies lead beyond the recording and description of these side effects. Our recently acquired knowledge of color vision changes induced by drugs however has led to the recognition of color vision as a quantifiable response suitable for investigating drug action. One of the aims of this Symposium Proceedings volume therefore is to view the retina as a pharmacodynamic model that can be used to elucidate and classify events occuring at receptors.

The retina is anatomically, biochemically and physiologically one of the most thoroughly investigated regions of the nervous system. It contains a variety of receptors, can be studied as an isolated organ and has an intermediate complexity between the peripheral nervous system and the CNS. Pharmacologists have much to do in this field before they can stand on a par with the biochemists and physiologists in understanding the events relevant to their own speciality, that occur in the retina and the significance that these may have with regard to the CNS and drug action at the molecular level. If this volume can help in this task then the hopes of the Editors and the efforts of all fellow colleagues in the University Clinic, Frankfurt am Main (R. Kirsten, A. H. Staib, R. G. Alken, A. Laßmann) and other institutions, who have made this symposium publication possible, will not have been in vain.

N. Rietbrock, B. G. Woodcock

Contents

Contemporary trends in the classification of the acquired colour vision defects

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Problems in classifying acquired colour vision defects have been recognised since the first systematic studies of such disturbances. The earliest efforts to formulate a classification were made in the second half of the 19th century by Galezowski (1868) in France, Mauthner (1881) in Austria and Bull (1883) in Germany using pigmentary tests.

From the late 1880's to the early 1920's, the study of the colour vision defects became a brilliant German speciality with first rank scientists such as von Helmholtz, Koenig, von Kries, Koellner, Simon, Nagel and Engelking. von Kries (1897) demonstrated the fundamental difference between the absorption systems that can be observed in acquired ocular pathology and the alteration systems associated with congenital anomalous trichromatism. Acquired blue-blindness was already accurately described by von Helmholtz and by Simon. Koellner (1912) summarized knowledge of the epoch in a classification of the acquired defects: this included a blue-yellow blindness for retinal diseases and a progressive red-green blindness leading to total colour blindness characteristic for diseases of the optical pathways from the inner retinal layers.

After the early 1920's the study of colour vision became more a speciality of Anglo-Saxon physicists, who concentrated on normal vision and congenital colour vision defects. The acquired defects were almost forgotten, except for a few german workers such as Helmbold in the 30's and Jaeger in the 50's, and the Japanese who also had inherited the teachings of the pre-First World War German school.

A new focus was born meanwhile in Western Europe with papers of Dubois-Poulsen in France from 1948, Jules Zanen in Belgium from 1953 and of myself also in Belgium from 1956.

Since the subject of this paper is the classification of the acquired colour vision defects, I will summarize my contributions of 1963 and 1964 and discuss them in the light of later research observations.

From 1957 to 1963 I used examination techniques of the old German school, namely the colorimeter of von Helmholtz, the anomaloscope of Nagel, colour denomination of spectral lights as done by Koellner, and also the Anglo-Saxon ways of determining the spectral luminosity curve, together with more clinical tools such as pseudo-isochromatic plates from various countries and especially Farnsworth's ranking tests, namely the Panel D-15 and 100 hue tests which I introduced for the assessment of acquired colour vision defects.

The systematic application of these colour vision tests in ocular and neuro-ophthalmic pathology allowed me to establish a new classification of the acquired colour vision defects. I showed that, besides Koellner's retinal blue-yellow defect and neural red-green defect, there is also a retinal red-green defect, that is characterized by a scotopisation of the spectral luminosity curve. I called this new defect Type I acquired red-green defectiveness because it resembles more the protan congenital defects. Koellner's neural defect, now Type II, resembles more the deutan congenital defects. Furthermore I subdivided the Type I red-green, Type II red-green and blue-yellow defects in trichromatic and dichromatic stages; moreover I grouped the embarrassing cases into a so-called defectiveness without prominent axis (including also the acquired achromatopsias) and verified the existence of other defects already described by the Germans as mild absorption systems, chromatopsias and colour agnosias. I suggested that the mechanisms of acquired colour vision defectiveness involve not only the von Kries absorption and reduction systems, but also other mechanisms such as excentration, mesopisation and scotopisation systems.

This classification is now more than 15 years old and is becoming slowly but surely obsolete owing to a large number of new discoveries. These have come from newer methods of examination including more adequate anomaloscopes such as that of Pickford-Nicolson and of Moreland and from new foveal and peripheral threshold methods for the assessment of the retinal colour vision mechanisms.

Before discussing advances made with these new methods, I should state that the first weak point of my system was that I did not determine spectral hue and saturation discrimination curves as was so well done at about the same time by Cox (1960/61) and by Jaeger and Grützner (1963), and later by Marré (1969). Jaeger and Grützner (1963) improved the definition of the red-green and blue-yellow defects by means of hue discrimination curves and careful neutral zone determinations. They criticized my subdivision into trichromatic and dichromatic stages with good reasons since we now know that in acquired defects, the number of necessary primaries can change, e.g. with the size of the observation field. Moreover, Marré (1978) pointed out that the same disease can give different types of defect and different authors considered different types of defect as typical for the same disease. These divergences were mainly attributable to an intrinsic tritan polarity of the Farnsworth tests.

Most of the proposed changes to my system however concerned blue-yellow defects. Jaeger and Grützner (1963) tried to establish subtypes of acquired blue-yellow defectiveness according to the behaviour of the spectral luminosity curve (either normal, or scotopized). By means of the assessment of the spectral luminosity curve I confirmed in 1970 that acquired blue-yellow defects can be due not only to diseases of the outer retinal layers, but also to pre-receptoral absorption of the shorter wavelengths as in cases of brown nuclear cataracts. Ohta (1970) however stressed that acquired blue-yellow defectiveness can also be due to optic nerve disease and this was not confined to juvenile dominant optic atrophy (the disease in which such a defect had already been described long ago by Jaeger). Pinckers (1971) subdivided acquired blue-yellow defectiveness into tritan and tetartan subtypes, as ascertained by means of the tests of Farnsworth. Finally,

Smith, Pokorny and Diddie (1978) firmly set a new subdivision of acquired blue-yellow defectiveness according to the presence or the absence of a shift of Rayleigh's match toward red: this shift chiefly occurs in central serous retinopathy and is thought to be due to a distortion of the photoreceptors as shown by the study of the Stiles-Crawford effect. This shift does not occur in other blue-yellow defects such as that due to glaucoma.

Of even more relevance are recent studies on the function of the retinal colour mechanisms using increment threshold techniques.

The background of such techniques are on the one hand the spectral π-mechanisms shown by Stiles (1939) by measurement of the increment threshold for an object of a given wavelength on a background of another wavelength (this technique reveals at least one rod mechanisms π_0, three blue mechanisms π_1, π_2 and π_3, a green mechanism π_4, and a red mechanism π_5), and on the other hand the three so-called "colour vision mechanisms" (in fact the approximate absorption curves of the three cone photopigments) evidenced

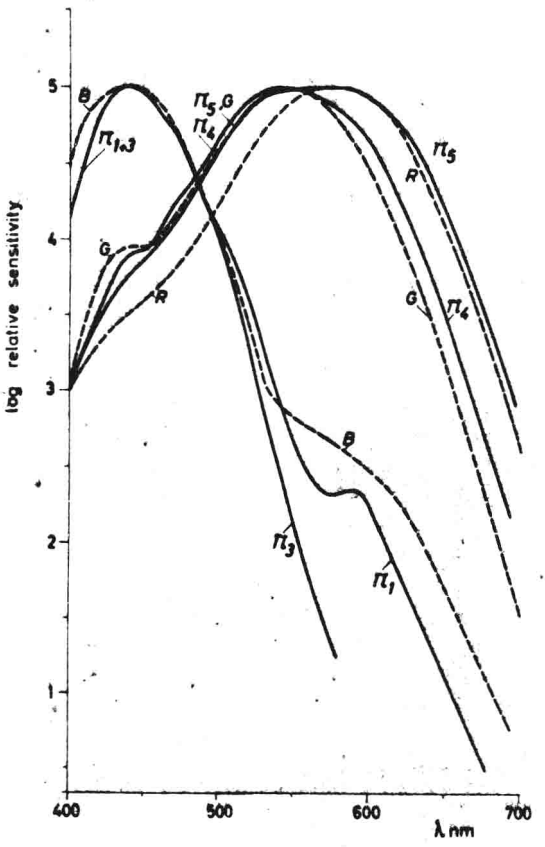

Fig. 1
Stiles π mechanisms (——) and Wald „colour vision mechanisms" (– – –). After Wald (1964).

by Wald (1964) by the determination of the threshold spectral sensitivity curves after bleaching two of the three photopic photopigments (the red-sensitive pigment is isolated by an intense broad band blue background, the green sensitive pigment by an intense purple background, and the blue-sensitive pigment by a still more intense yellow background). It must be stressed that there is no sharp distinction between the technique used by Stiles and that used by Wald. These differ only in terms of spectral distribution and intensity level of the coloured background lights. Quite different results are given by the techniques of measurement of similar spectral increment thresholds on a white background. Indeed, whilst the spectral luminosity curves obtained by the flicker and minimally distinct border techniques of heterochromatic matching are unimodal and smooth being almost exclusively derived from the achromatic brightness signals, the spectral increment threshold sensitivity curves obtained on a white background present different humps and dips because there is a contribution from antagonistic chromatic signals (Harwerth and Sperling, 1971; King-Smith and Carden, 1976). Thus, compared with a white background, the use of coloured backgrounds allows a clear separation of the colour vision mechanisms, but at the same time it obscures physiological relationships between them.

Wald's method was extensively applied to ocular pathology by Marion Marré. The results published in her first series of papers (1969–1978) were a hard blow to all systems of classification of the acquired colour vision defects as the author stated that all retinal or optic nerve diseases gave the same pattern, namely an isolated reduction of the blue mechanism followed by a reduction of all three mechanisms. Her material consisted of 33 cases of acquired pathology with foveolar fixation. In a later paper (1978) she also studied cases with extrafoveolar fixation. She concluded that in the cases of extramacular fixation the blue mechanism turns out to be less affected, but again without substantial differences between the retinal and optic nerve pathology; it is only in the cases of extrafoveal with intramacular fixation that the diseases of the retina seem to affect the blue mechanism to a greater extent.

The application of Stiles' method was more fruitful for the classification of the acquired defects than that of Wald's method. Indeed, interesting results were presented at the meetings of the International Research Group on Colour Vision Deficiencies and of the International Perimetric Society by various authors, principally Hansen, Vola, Moreland and Kitahara. They all use perimeters and thus determined π-functions foveally as well as peripherally. Hansen, for example found an abnormal green mechanism in cone dystrophies (1974) and an early loss of the blue mechanism in retinitis pigmentosa (1977).

Determination of spectral increment sensitivity curves on white background have provided essentially similar results. Foveal measurements in maxwellian view have been applied by the Manchester school in particular (King-Smith, Zisman, Bhargava, Alvarez), whereas foveal and peripheral measurements by means of perimeters calibrated in energies have been used by others (Verriest and Uvijls, 1977). After determination of the conditions in which the individual colour vision mechanisms are normally most apparent by their antagonism (King-Smith and Carden, 1976), the method allows recognition not only of diseases in which there is a selective loss of the blue mechanism (as in retinitis

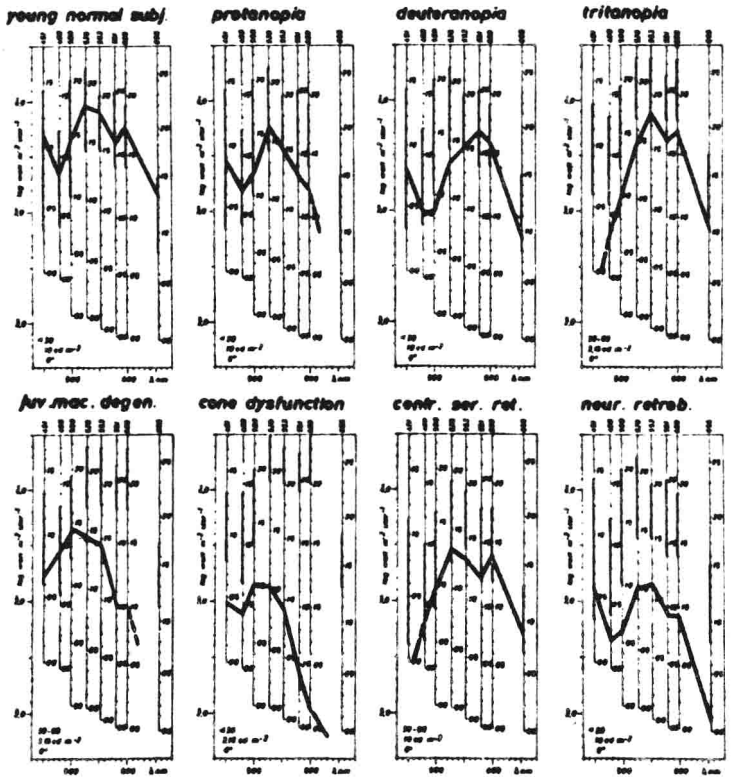

Fig. 2 Spectral increment threshold sensitivity curves on the white background of the Tübingen perimeter. After Verriest and Uvijls (1977).

pigmentosa) or of the red mechanism (as in juvenile macular degeneration), but also of two entirely new conditions. One is a loss of antagonism between the colour vision mechanisms so that the threshold sensitivity curve becomes more or less unimodal (first described by King-Smith, Kranda and Wood, 1976, and later by Zisman, King-Smith and Bhargava, 1978, especially in tobacco amblyopia and by Zrenner and Krüger, 1980, in ethambutol intoxication) and the other is a reverse situation, namely an augmentation of the antagonism between the green and red mechanisms, so that the spectral threshold sensitivity curve presents a deeper dip between the green and red humps. This last condition was first described by Sperling, Piantanida and Garrett (1976) and was found again by Zisman (1978) in a case of cassava intoxication.

There are thus good indications that the earlier, purely descriptive and therefore less accurate classifications of the acquired colour vision defects will be soon more or less replaced by a more fundamental classification based on the real etiological mechanisms. It is important that the older and newer methods of examination are applied side by side in

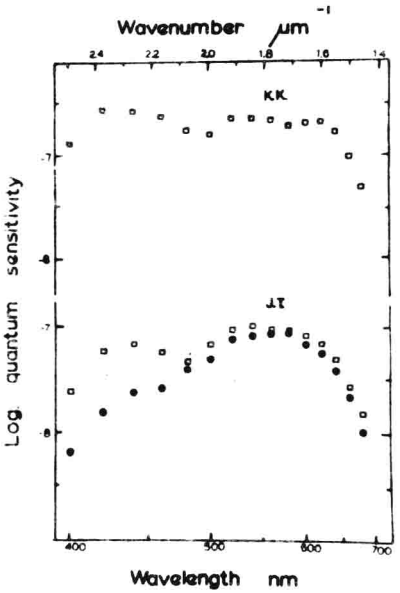

Fig. 3

Spectral increment threshold sensitivity curves on a white background, including an eye with loss of opponency. After King-Smith, Kranda and Wood (1976).

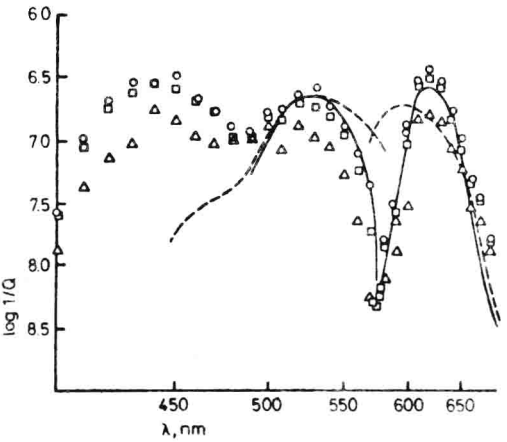

Fig. 4

Spectral increment threshold sensitivity curve on a white background in a case with increased opponency. After Sperling, Piantanida and Garrett (1976).

the same patient so that we can compare the older and the newer classification systems. As this meeting is devoted to colour vision in clinical pharmacology, I would like to end my talk by stressing that the newer psychophysical methods of studying the acquired defects of colour vision, by means of the measurement of spectral threshold sensitivity curves, could be applied not only to humans, but also to trained monkeys, as Harwerth and Sperling (1971) have done in studies on the retinal damage due to excessive exposures to light. Basically similar experimental methods could be applied for studying the effects of drugs on the eye.

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An introduction to the neurophysiological basis of color vision and its clinical applications

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Contents:

A The neurophysiological basis of color vision

There are many unresolved questions regarding how the outer physical world is transferred to our inner world, a process we are used to calling perception. Even though, in many cases, no definite answers can be given, an attempt shall be made to give a survey of the present knowledge on neurophysiological aspects of color vision and to outline several ideas still being discussed. Since I was asked to address in this lecture especially those readers who are not routinely dealing with neurophysiological problems, I will

discuss not only the physiological mechanisms of our central nervous system, but also the morphological structures which build up our environment's image in the form of nerve impulses. I shall demonstrate that, in this process, the retina plays a considerably larger part than is usually mentioned in textbooks. Most of the mechanisms discussed here were investigated in our laboratory during the last few years, either in studies on higher mammals and nonhuman primates or (in the above named clinical department) on man.

1 The outstanding abilities of our visual system

After some comments on the outstanding abilities of our visual system, the first part of this lecture shall introduce the several retinal cell types and their function.

The visual system's goal is to detect objects in a permanently changing environment. It has to be able to adapt to an enormous range of light intensity levels, from a moonless night to a one hundred thousand million times brighter sunny beach on a summer midday; there is no photographic emulsion covering such a range. Moreover, the visual system has to resolve fine details (lying only a few seconds of arc apart) without sacrificing its large visual area of more than 100° in diameter. There is no single photographic system which can perform this task. Moreover, the visual system has to process its information very quickly so as to maintain 'real time'. The inner image has to be brought up-to-date, some ten times per second, to permit the organism to react. Just recall the situation of somebody who plays table tennis and try to imagine the flow of visual information necessary to hit the almost invisible shape of a fast moving ball.

At the entry to the retina, the information present is estimated at 10^7 bit/s; however, the central nervous system can process only up to 40 bit/s. A selective process able to extract the 40 most significant bits/s at the output of the retina obviously requires a large amount of neuronal processing. That a neuronal "convergence" takes place can be inferred from the fact that several 100 million rod photoreceptors (most active in dusk conditions) and 7–10 million cone photoreceptors (most active in daylight conditions) have to share the 1 million available fibres of the optic nerve which carries the signals to the ganglion geniculatum laterale which then distributes them to the visual cortex. However, peripheral and central parts of the retina process information quite differently as will be shown below. The retinal periphery only needs to signal *that* there is an object of interest; the central fovea has to be directed to this object in order to analyze *what* type of object it is.

Color vision plays an important part in this analysis. A system which is not only able to calculate the *number* of light quanta (brightness) but also to utilize their wavelength (and thus signals hue), can detect many more objects than a color-blind one. In a natural environment, *moving* objects can be detected just as well by a color-blind system, since e.g. a bird flying over the trees permanently changes its brightness contrast relative to the background against which it is viewed. *Static* objects, such as a motionless sitting bird, however, very often reflect the same number of quanta as their background and are therefore invisible to pure brightness-detecting systems; only analysis of spectral differences of object and background, enables the visual system to easily detect such an object,

e.g. a red bird in a green tree. Consequently, color vision was not developed to beautify our outer physical world but serves as an evolutionary important selection criterion, namely to detect objects of equal-luminance by their wavelength differences. For orientation in our environment, there are not only twenty simultaneously detectable steps of brightness available, but also 200 discernable hues of the sun's spectrum. Together with the possibility of changing a color's saturation by overlaying white light, we can perceive about 7–10 million different colors. The probability of detecting an object, even though its luminance is equal to that of its background, is thereby greatly increased.

The relationship between brightness, hue and saturation, and their correlation to wavelength and energy of light, can be described in terms of color metrics. A simple model is given in Fig. 1 by the so-called Munsell-Tree, where brightness gradients appear at different heights, hue gradients in different branches and saturation gradients along the branches. A more quantitative standardized model was developed in the "Deutsche Industrie-Norm" DIN 5033; for an introduction to these problems the reader is referred to Scheibner (1969, 1976a, b).

It should, however, be made very clear that color is not so much a characteristic of the object than of the observer's neuronal system. Red and green lights can be mixed to appear like spectral yellow, even though they do not contain a single quantum of the sun's yellow spectral band. Physically, many different conditions can produce the same color perception depending on the properties of the receiving neuronal system (see Gouras and Zrenner 1981a). How does this receiving system work? In man and in higher primates, the validity of the Young-Helmholtz theory (see Helmholtz 1860/67) is unquestioned: There are three different types of cones with specific photopigments, with the maximum of absorption at three different spectral loci (Fig. 2). With the methods of modern fundus-reflectometry (Rushton, 1975) and microspectrophotometry (Marks, et al., 1964; Bowmaker and Dartnall 1980), the absorption maxima were found at 440 nm (blue), 530 nm (green) and 570 nm (orange/red). Note, however, that the pigment absorption curves are broad and relatively flat; therefore, light quanta of any wavelength – if sufficiently numerous – can produce photopigment reactions and thereby trigger a neuronal signal.

2 The structure of the retina

What is the structure of this receiver? As shown in Fig. 3, the outer segment of a receptor contains many discs (about 1000) which are either floating (in cones) or partially attached to the outer membrane (in rods); each disc contains up to 10 million pigment molecules; each light quantum is able to isomerize one pigment molecule (for a review concerning these questions see Brindley, 1970). The absorption of one light quantum causes release of about 100 Ca^{++}ions, (see Hagins, 1979) probably acting as a modulator and decreasing the sodium conductance of the receptor membrane.

Illumination of receptors hyperpolarizes the outer segment so that the phototransduction results in a negatively directed receptor potential. Since a single cone contains only one type of pigment it cannot signal information about the wavelength of a light quantum; it is therefore necessary to process the signals of different cone types in subsequent

etinal neurons to extract information about color. A schematical drawing is shown in Fig 4, based on several studies of Nelson and Kolb (see reference section). The cone eceptor pedicles (C) are connected by horizontal cells Ah and Bh, the latter having a pecial axon terminal (at) which collects signals from rods (r). Beyond the rod bipolar ell (rb) two types of cone bipolars, the invaginating (ib) and the flat type (fb) as they re called due to their way of contacting cone pedicles, carry the information from the outer plexiform layer (OPL) through the inner nuclear layer (INL) to the inner plexiform yer (IPL). As demonstrated by Nelson et al., (1978), the invaginating type is depolarized y light (on-neuron) while the flat type is hyperpolarized by light (off-neuron); this functional difference is also represented in clear morphological separations in the IPL. On-polar cells (ib) contact ganglion cells (g) in the inner two-thirds of the IPL, while off-polar cells (fb) exclusively make contacts in the outer third of the IPL. Several types of amacrine cells (A) provide lateral connections in the IPL: type AI mainly for the cone pathways, type AII for rod pathways. Note that rod bipolars do not make contact directly with ganglion cells (g), but only through the intermediary action of an AII amacrine cell (Kolb et al., 1976, Kolb and Famiglietti, 1976). Specific types of so-called interplexiform amacrine cells (i) can make direct contacts between the receptor layer and the ganglion cell layer. Several groups of ganglion cells can be discerned:

a) a group with large cell bodies (gI), fast conduction-velocity, large dendritic and receptive field size exhibiting short transient (phasic) responses (Gouras, 1969); in cat also called Y-cells;

b) a group of smaller ganglion cells (gII), with lower conduction velocity, smaller dendritic and receptive field sizes, sustained (tonic) responses (in cat also called X-cells);

c) an intermediary group (gIII).

For a more morphological classification see Boycott and Wässle (1974).

Chromatic signals are mainly carried by tonic cells, the functions of which will be discussed below. By injecting dyes into the cell through the microelectrode, it was possible in recent years to correlate morphology and functions also in higher mammals, especially in cat retina (e.g. Nelson, 1977) and thereby to discover specific features of retinal circuitry (Zrenner et al., 1983).

3 Electrophysiological recordings in Rhesus monkeys

A setup designed to record electrical signals from retinal cells is shown in Fig. 5: A glass micropipette filled with a conducting medium (e.g. 3 M KCL) is inserted through a scleral hole into the eye of anesthetized paralyzed experimental animals. A hydraulic system enables the electrode to advance or be retracted by steps of a few micrometers without introducing major mechanical disturbance. The signal is amplified, filtered, viewed on an oscilloscope and recorded on magnetic tape. Position and movement of the electrode can be viewed through a modified clinical fundus-camera which is also used to project test and adaptation lights onto the retina. The wavelength, energy, size of stimulation and length interval are controlled by an electronic, partially computer-controlled, system (see Zrenner and Baier, 1978).