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Personal practice

The electroretinogram

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SUMMARY The electroretinogram, findings, in response to a flash stimulus, was recorded from a skin electrode placed on the bridge of the nose in 4465 infants and children seen over a 10 year period. The electroretinogram was combined with a flash visual evoked potential. From this total, the electroretinographic findings in 240 patients, aged 1 day to 17 years, without suspected retinal pathology and with a normal visual evoked potential, were used as controls and normal electroretinographic parameters of different age groups defined.

There were 332 patients who showed an absent or very reduced amplitude electroretinogram. They were divided into primarily ocular disorders (n=195), neurodegenerative disorders (n=94), and various syndromes (n=43). Fundus examination did not always show any obvious abnormalities. The use of this simple and reliable technique for recording the electroretinogram made it possible to include this investigation as a routine procedure without the need for sedation in infants and uncooperative children. Electroretinographic studies, especially when combined with visual evoked potentials, and in some cases electroencephalography, may aid diagnosis in a wide variety of paediatric conditions, many of which have genetic implications.

Electroretinography measures the field potential of the retina in response to a flash of light and can be used clinically to assess retinal function (mainly rods and cones). The electroretinogram may show an abnormally small or absent response in retinal disorders even when in some instances there are no detectable abnormalities on ophthalmoscopic examination. In children there is a wide range of disorders in which the retina may be affected. Such disorders may be congenital or acquired and some evolve over a period of time. They include not only primarily ophthalmological disorders but also some systemic disorders or syndromes and certain neurodegenerative diseases.

In the uncooperative infant or child it is important to be able to record the electroretinogram reliably without the need for sedation or anaesthesia. Over the last 20 years a simple method using averaging techniques and recording from an electrode placed on the bridge of the nose has been developed in the department of clinical neurophysiology at the Hospital for Sick Children and some normal electroretinographic parameters have been published.[1] Recording of the electroretinogram has been combined with the cortical visual evoked potential and normal findings for the flash visual evoked potential at different ages have been reported.[2] The maturation of the electroretinogram, in response to a flash of light, and particularly from birth to 12 months, has not previously been described in any detail particularly with this technique.

In this study the normal electroretinographic parameters at different ages from birth to 17 years have been measured and all patients seen over a 10 year period showing a very reduced or absent response have been collected and grouped into diagnostic categories, in an attempt to give a comprehensive range of paediatric disorders in which an appreciable reduction or loss of the electroretinogram may occur.

Patients and methods

Over a 10 year period, 1977–86, 5572 electroretinographic recordings (combined with visual evoked potentials) were made on 4465 patients referred to the department of clinical neurophysiology. Before this period, criteria of normality of the flash electro-

retinogram with the same technique was established in our laboratory in a series of 62 children aged 1–14 years with congenital heart disease. Although there have been only some changes in the averaging apparatus used since that time, it was considered worthwhile to measure the electroretinographic parameters in a larger number of children including infants less than 1 year and compare findings at different ages. For this purpose 240 infants and children from birth to 17 years of age were selected from patients seen in the last 10 year period. Although many of these patients had some neurological problems, mainly seizure disorders or retardation, or both, none had known ocular pathology and all had a normal flash visual evoked potential. These patients were usually more difficult to test than normal infants and children and therefore more comparable with patient groups investigated for ophthalmological problems.

From the total patients seen over this 10 year period, 332 were found to have an abnormal electroretinographic response, which was defined as absent or very reduced in amplitude (to less than half the expected size for age and conditions of testing). It should be noted that the number of patients with an abnormal electroretinogram was very much smaller than the number with an abnormal visual evoked potential.

Some details of techniques used in this department for recording the averaged skin electroretinogram (together with visual evoked potential) have previously been reported.[3 4] In brief, a silver disc electroencephalographic electrode was placed on the bridge of the nose and secured with sticky paper tape. Contact was made with electrode jelly and impedances of less than 2 Kohms obtained. An electrode placed over the vertex (using collodion) was used as a reference. A stroboscope (SLE) (emitting a flash set to produce 0·12 joules) was hand held close to the eyes (5·10 cm) and any head movements quickly followed. The room was not darkened during the procedure. Stimulation was at a rate of approximately 2/second except in infants under 12 months of age when slower rates were used. All children and infants were awake with the eyes open for as much of the time as possible. Great care was taken to exclude signals contaminated with movement artefacts or muscle action potentials and it was often necessary to interrupt and restart the collection of averaged data to achieve this. Ploys such as singing or tapping the glass of the lamp were used to keep the child still and quiet when necessary. Simultaneous bilateral eye stimulation was always carried out and, if a unilateral problem was suspected, monocular stimulation was achieved by holding a pad over the other eye. Many patients, especially young ones, had repeat studies to check maturation and progression of any disorder.

The electroretinogram was always recorded simultaneously with the flash visual evoked potential (derived from the mid occipital and right and left posterior temporal regions, also referred to the vertex). All signals were amplified using a Grass electroencephalograph machine with bandwidth of 0·3–100 Hz. Averaging was carried out using a PDP 11/40 general purpose computer with in house programs. At least 100 responses were averaged over a 250 ms epoch and repeated several times to ensure consistent findings. All patients had an electroencephalogram immediately before the electroretinogram and visual evoked potential investigations.

Results

NORMAL PARAMETERS

The averaged electoretinogram in response to a flash stimulus was recorded as a negative/positive complex ('a' and 'b' waves) of similar waveform though approximately one 10th the amplitude of that recorded with a corneal electrode using the same intensity stimulus.[1] The amplitude and duration of the components of the electroretinogram at different ages with the eyes open (bilateral stimula-

Table 1 *Normal parameters of electroretinogram at different ages*

Age (n=30)	*Mean (2SD) amplitude 'a' (uV)*	*Mean (2SD) duration 'a' (ms)*	*Mean (2SD) amplitude 'a/b' (uV)*	*Mean (2SD) duration 'a/b' (ms)*
0–4 Weeks	4·0 (3·20)	27·5 (7·64)	8·0 (6·54)	54·0 (17·58)
5–12 Weeks	6·0 (4·54)	25·0 (7·94)	12·5 (8·98)	48·0 (14·72)
3–5 Months	8·7 (5·22)	25·0 (7·26)	17·0 (9·06)	48·7 (18·60)
6–11 Months	10·0 (5·36)	25·0 (5·46)	21·7 (11·42)	46·5 (11·86)
12–23 Months	11·4 (4·22)	25·0 (6·30)	25·0 (11·72)	43·3 (7·90)
2–4 Years	13·0 (7·32)	25·0 (4·74)	25·0 (11·72)	43·3 (7·90)
5–10 Years	13·5 (7·28)	24·8 (4·80)	31·7 (17·92)	44·9 (13·6)
11–17 Years	13·3 (9·46)	24·5 (4·80)	29·3 (16·90)	44·1 (11·70)

tion) are listed in table 1. It can be seen that in the first month of life the electroretinogram is recordable with this technique, though the response is of very small amplitude and somewhat long duration. The amplitude progressively increases and the duration decreases and by 1–2 years of age are of relatively constant values (similar to those previously reported[1]). There is quite a wide individual variation in amplitude, however, especially in the older child as can be seen from the standard deviations given in table 1.

Representative electroretinographic records (bilateral stimulation) at different ages are shown in fig 1. The electroretinographic response from the same electrode with monocular stimulation is approximately half the size seen with bilateral

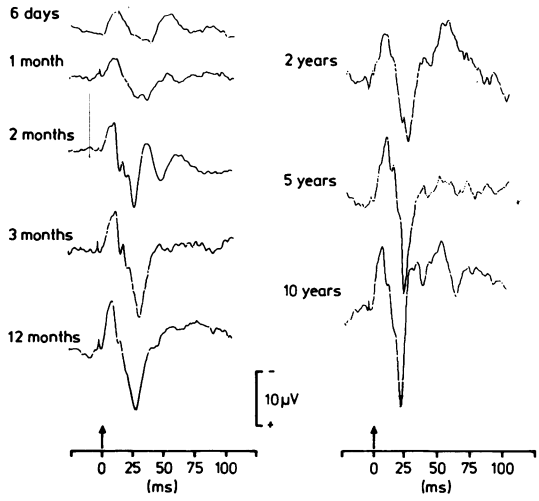

Fig 1 *Examples of normal electroretinographic findings at different ages with bilateral stimulation. Note the increase in amplitude of the 'a/b' complex, occurring over the first 50 ms after the flash stimulus (arrow), up to the age of 12 months.*

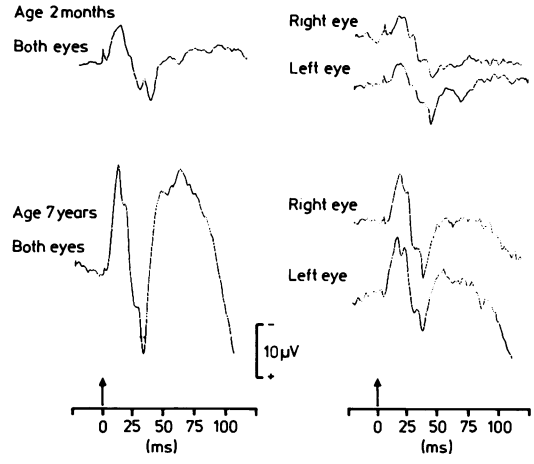

Fig 2 *Comparison of the electroretinogram with bilateral stimulation and monocular stimulation (covering one eye) in a young infant and child. Note the reduced amplitude of the 'a/b' complex with monocular stimulation but similarity between responses from each eye.*

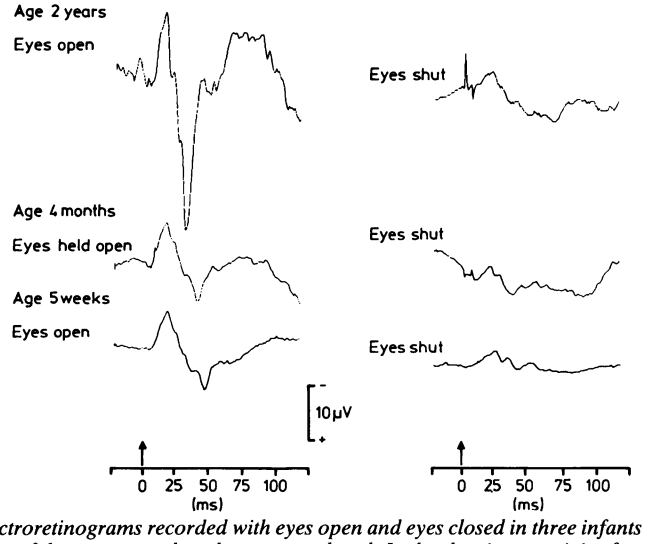

Fig 3 *Comparison of electroretinograms recorded with eyes open and eyes closed in three infants of different ages. There is an appreciable degradation of the response when the eyes are closed. In the sleeping state it is often possible to hold the eyes open and record the electroretinogram satisfactorily.*

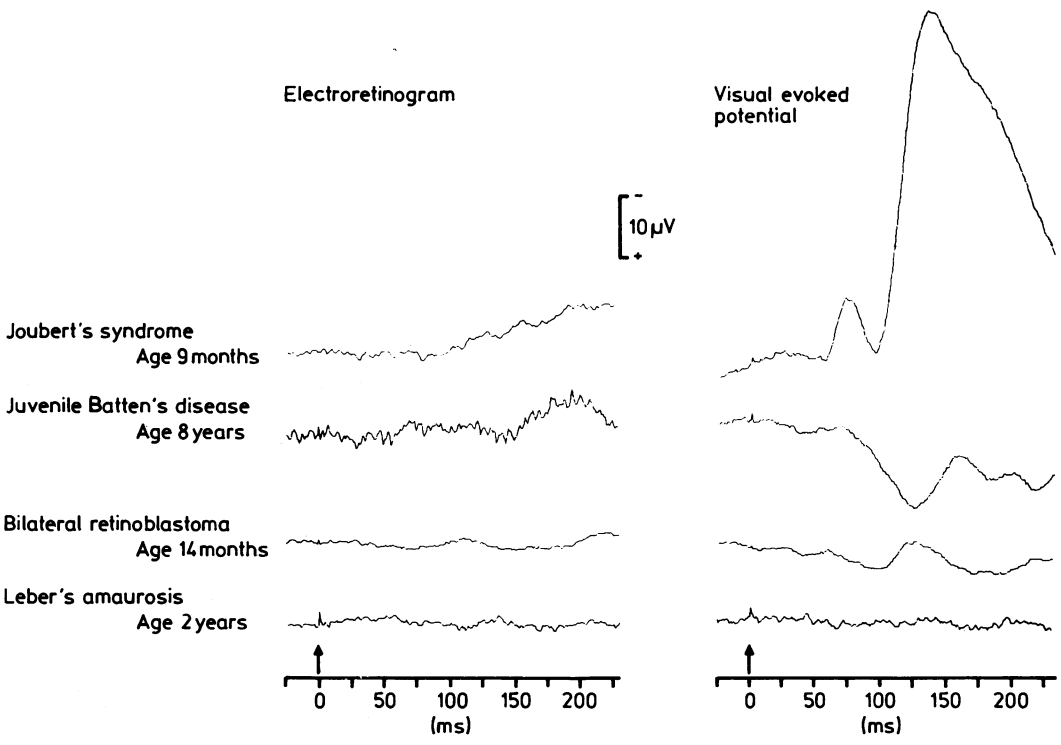

Fig 4 *Four children with an absent electroretinogram related to different conditions. Note the different visual evoked potential findings with a normal visual evoked potential seen in the infant with Joubert's syndrome and loss of main early negative component in the juvenile Batten's and retinoblastoma patients. The visual evoked potential is absent in the patient with Leber's amaurosis. The visual evoked potential findings may vary in all these conditions.*

stimulation (fig 2). If the eyes are shut a smaller and more prolonged response is recorded (fig 3) and ideally the response is recorded with the eyes open even if held open during the sleeping state (fig 3).

ABNORMAL FINDINGS

The 332 cases in whom the electroretinographic response was absent or appreciably reduced in amplitude have been somewhat arbitrarily divided into primarily ocular disease (table 2), neurodegenerative disorders (table 3), and various syndromes (table 4). Some examples of combined electroretinograph and visual evoked potential findings in some of these disorders are shown in fig 4.

Discussion

The technique for recording the flash electroretinogram as described has proved simple and reliable even in patients unable to cooperate. Some other workers have preferred to use skin electrodes placed under each eye that enables recording a separate electroretinogram from each eye. In our experience, however, these electrodes are not so well tolerated by the child who is young or retarded, or both, as a single electrode on the bridge of the nose. Although the electroretinogram thus recorded is the summed response from both eyes, abnormalities in most of the conditions described affect the retina of both eyes. A reduced amplitude electroretinographic response with bilateral stimulation will often suggest a monocular retinal disorder. If a unilateral retinal problem is suspected, it is more useful to cover one eye and not only record the monocular response but also the monocular cortical visual evoked potential. As the optic pathways from each eye pass to the visual cortex of both hemispheres, monocular stimulation is necessary if the integrity of the visual pathways from each eye to the brain is to be assessed.

Most patients with abnormalities on electroretinography show some fundus changes suggestive of a retinopathy and the fundal appearance of retinitis

Table 2 *Ocular disorders*

	No of patients
Dystrophies:	
Leber's amaurosis	60
'Retinal dystrophy'	19
Rod/cone dystrophy	11
Retinitis pigmentosa	9
Stargardt's disease	1
Gyrate atrophy	1
Choroideraemia	1
Malformations:	
Microphthalmos (with or without other)	23
Coloboma	5
Persistent hyperplastic primary vitreous	3
Retinal fold and hyaloid remnant	1
Retinal detachment	11
Retinopathy of prematurity	21
Retinitis/chorioretinitis:	
Congenital	2
Acquired	
Cytomegalovirus	2
Chickenpox	1
AIDS	1
Unknown	1
Retinoblastoma	3
Vascular:	
Retinal haemorrhage	3
Injury	4
Postsurgical	3
Osteopetrosis	1
Undiagnosed:	
With cataracts	5
Others	3
Total	195

Table 3 *Neurodegenerative disorders*

	No of patients
Batten's disease:	
Infantile	1
Late infantile	16
Juvenile	32
Variant forms	8
Mucopolysaccharidoses:	
Sanfilippo	2
Scheie	1
Hurler	1
Unknown	1
Mucolipidoses type IV	2
Hallervorden-Spatz disease	1
Mitochondrial cytopathy	7
Peroxisome disorders:	
Infantile Refsum	2
Zellweger syndrome	2
Spinocerebellar degenerations	5
Undiagnosed	13
Total	94

Table 4 *Syndromes*

	No of patients
Aicardi	1
CHARGE association	1
Cockayne	1
Ellis-van Creveld	1
Jeune	1
Joubert	2
Laurence-Moon-Biedl	9
Norrie's disease	6
Senior	4
Sjögren-Larssen	1
Usher	3
Walker-Warburg (HARD±E)	2
Undiagnosed	11
Total	43

pigmentosa is well known. This is not always the case, however, most notably in the young patient with Leber's amaurosis.[5] Conversely some retinopathies—for example, rubella—do not show abnormalities on electroretinography and visual function is not always compromised.[6] In patients who are difficult to examine clinically, the presence of a normal electroretinogram is some reassurance that there is no appreciable loss of function of outer retinal layers. In the presence of cataract, fundus examination may be limited. In our experience the flash electroretinogram is normal in most patients with cataracts unless retinal pathology is present and an abnormally reduced or absent electroretinographic response in the presence of cataract is indicative of retinal pathology. The few cases of cataracts with abnormal findings listed in table 2 are presumed to have other unidentified ocular disease. Nystagmus was a very common symptom in many patients, with or without retinal pathology, and has not been considered as a separate entity.

The flash electroretinogram is mainly derived from peripheral photoreceptors and its absence does not necessarily imply that all retinal function has been lost. As the flash visual evoked potential is a mainly macular response, the combined recording of an electroretinogram and visual evoked potential may be helpful in distinguishing between peripheral and macular retinal problems. Thus an absent electroretinographic response can be associated with a normal visual evoked potential in patients with some preservation of macular function (fig 4) and is usually associated with reasonable vision.

The commonest diagnosis in the primary ocular group was a retinal dystrophy. The diagnosis of unclassified retinal dystrophy can only be made by exclusion of other known causes for reduced vision and retinopathy by biochemical screening (amino

acids, phytanic acid, urine osmolality, creatinine clearance, mucopolysaccharides, blood lipids). The cone/rod dystrophies are considered as a distinct subgroup. In this study the electroretinogram has been recorded under photopic conditions and, although, even with a non-corneal electrode, rod and cone responses can be distinguished using flicker fusion or varying spectral frequencies of stimulation, this has not been routinely carried out.

The most commonly diagnosed retinal dystrophy was Leber's amaurosis, first described by Leber in 1869,[7] in infants who before the age of 1 year show appreciably reduced vision, nystagmus, and poor pupillary reactions. It is regarded as having an autosomal recessive mode of inheritance. In 1954 Franceschetti and Dieterlé added an absent or appreciably reduced electroretinographic response to the diagnostic criteria.[8] The fundus appearance varies from normal to a retinal dystrophy like picture. The disease can have systemic associations such as renal and neurological disease.[9] Because of the varied presenting clinical signs and differing fundus appearances, the electroretinographic findings have been considered crucial in making the correct diagnosis.[10]

As the electroretinogram shows a mass retinal response to light stimulation, it is obvious that any condition that destroys a large amount of retina such as gyrate atrophy and choroideraemia as well as a large retinoblastoma will affect the response. In coloboma of the eye there is thought to be defective closure of the fetal fissure, leaving a defect which in the retina is replaced by glial and fibrous tissue. Depending on the size of the coloboma and therefore the amount of retina affected, the electroretinogram may or may not be reduced. Bilateral macular dysplasia ('colobomata') has been described in association with retinal dystrophy,[11] with the retinal responses disproportionately small to the size of the coloboma.

In the more severe forms of retinopathy of prematurity in which there is an abnormal vascularisation of the retina, the retina becomes detached and the electroretinographic response is appreciably reduced. The retina may also became detached in persistent hyperplastic primary vitreous and so reduce the electroretinogram. In severe microphthalmia the retina is poorly developed, especially as it is frequently associated with a coloboma, explaining both the poor vision and the reduced electroretinogram. In primarily macular disorders such as Stargardt's disease, enough peripheral retina may be affected to reduce the response. Surgical procedures including resection of an optic nerve glioma may compromise the ocular circulation and thus account for electroretinographic abnormalities in such cases.

Hoyt and Billson first described a small or absent electroretinogram in three patients with the infantile form of osteopetrosis (an abnormal response has only been found in one of six patients we have examined), despite a normal fundus appearance.[12] They suggested that visual loss in these patients may be the result of retinal degeneration rather than solely due to optic atrophy, although the reason for any retinal pathology is not clear.

In our series by far the largest group of neurodegenerative disorders showing electroretinographic abnormalities were the various types of Batten's disease (neuronal ceroid lipofuscinosis). Diagnosis can be confirmed by histological examination only (as no biochemical defect has been identified) and combined clinical neurophysiological assessment has proved of considerable value in suggesting the diagnosis.[13] In all types of Batten's disease the electroretinogram is affected at a relatively early stage, particularly in the juvenile form which usually presents at 5 to 6 years of age with visual problems. It should be noted that the flash electroretinogram is not affected in the various types of gangliosidoses as only the ganglion cell layer of the retina is involved in these disorders.[14] While the electroretinographic findings may not be important in the diagnosis of the mucopolysaccharidoses, it may often be worthwhile carrying out electroretinographic studies to monitor any progression of retinal dysfunction especially in the presence of cataracts. Reduction of the electroretinographic response, however, may be helpful in the diagnosis of rarer disorders such as mucolipidosis type IV[15] and Hallervorden-Spatz disease, and in our experience progressive changes may occur over a number of years in both these diseases. In the newly recognised peroxisome disorders[16] it seems that electroretinographic abnormalities may be present from an early age,[17] as we have found in infantile Refsum's disease and some cases of Zellweger's syndrome. An absent electroretinogram has been reported in infantile adrenoleucodystrophy,[18] although as yet we have not seen any cases with this diagnosis.

The diagnosis of a syndrome is based on the recognition of a pattern of associated anomalies. In some of the syndromes listed in table 4 there is an associated pigmentary retinopathy as for example, Laurence-Moon-Biedl, Senior's[19] and Joubert's[20] syndromes. There are also causes for a reduced response other than in a retinopathy as for example, coloboma in CHARGE syndrome,[21] chorioretinal lacunae in Aicardi's syndrome,[22] retinal malformations in Norrie's disease,[23] and retinal dysplasia in Walker-Warburg's syndrome.[24]

In the progressive neurological disorders and in many of the syndromes listed, the electroretino-

gram is progressively reduced in amplitude over the course of months or years, usually paralleling changes in vision (and also in visual evoked potentials). In conditions such as eye injury (including non-accidental injuries) and retinal haemorrhages (secondary to for example, hypertension or leukaemia), the extent of retinal abnormality is variable and determines whether or not the electroretinogram is affected. This is also the case in infections whether congenital, such as toxoplasmosis or cytomegalovirus, or acquired (seen mainly in immunosuppressed patients in our series). It should also be noted that in most of the syndromes described, retinal involvement (and consequent electroretinographic abnormality) is not invariable. In a disorder such as mitochondrial cytopathy, which has such a very variable clinical expression, it is not surprising that less than half the cases we have seen show electroretinographic abnormalities.[25] Associated deafness may occur in mitochondrial cytopathy and in some other conditions as for example, Usher's and Senior's syndromes and infantile Refsum's disease among others.[26] The auditory problem can be documented using brain stem auditory evoked potentials in the very young or uncooperative child, and the combination of abnormalities found on electroretinography and brain stem auditory evoked potentials may be important in delineating some of these disorders. In addition the presence and type of any electroencephalographic abnormalities may also be important in suggesting the nature of any associated cerebral involvement in some of the conditions described especially in some of the neurodegenerative disorders.

Recording of the flash electroretinogram appears to have been a somewhat neglected investigation, especially in children, perhaps because it has generally been believed that it is only possible to carry out using corneal electrodes under general anaesthesia. As outlined in this study, however, reliable recordings can be obtained as a routine procedure in the waking state, without any need for cooperation, and avoiding anaesthetic risks. Most departments of clinical neurophysiology now have averaging equipment available and recording the electroretinogram from skin electrodes is quite feasible using averaging techniques. There are advantages in electroretinography being carried out in clinical neurophysiology units where evoked potential studies and electroencephalography can also be carried out as appropriate. The integrated reults often give much more information than any one test alone, especially in disorders that may involve the brain or auditory pathways, or both.

It is appreciated that the disorders discussed in this survey do not comprise an exhaustive list of all paediatric conditions in which the electroretinogram may be affected. Furthermore over the 10 year period of this survey the diagnostic categories have widened and some patients seen in the earlier years and, in particular, patients diagnosed as Leber's amaurosis would now be given a different diagnostic label as awareness of conditions such as Joubert's syndrome, cone dystrophies, and congenital stationary night blindness have been appreciated. While it is not claimed that the flash electroretinogram recorded with this technique can detect subtle or early retinal involvement, the results show that the finding of a reduced or absent response is often essential in the diagnosis of a wide variety of not only ocular problems but also some neurodegenerative conditions and is a pointer towards the identification of some syndromes. As there are genetic implications in a number of these disorders, the importance of a correct and early diagnosis cannot be over emphasised.

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