3 *Photosensitive Epilepsy in Man and the Baboon:*

Integration of pharmacological and psychophysical evidence

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This chapter concerns the two closely similar syndromes of photosensitive epilepsy occurring in man (reviewed by Newmark and Penry, 1979) and the

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Senegalese baboon, *Papio papio*, (Naquet and Meldrum, 1972). In man evidence derives principally from gross EEG studies and from detailed psychophysical investigations (see Wilkins *et al.*, 1980). In the baboon, *Papio papio*, available sources of evidence include depth recordings with gross electrodes (e.g. Fischer-Williams *et al.*, 1968) and more recent recordings of single cortical units (Menini *et al.*, 1982; Silva-Comte *et al.*, 1982).

Data derived from pharmacological and pathological experiments in baboons and other animal models of epilepsy are used to attempt a (speculative) synthesis relating to cellular mechanisms responsible for epileptogenesis in photosensitive seizures.

I. PHOTOCONVULSIVE RESPONSE V. PHOTOMYOCLONUS

"Photosensitive epilepsy" occurs in about 3% of patients with epilepsy, principally those with epilepsy of the primary generalized type. The term refers to any clinical syndrome in which attacks are triggered by visual stimulation, whether flashes of light or patterns. Such a diagnosis may be proposed on the basis of the clinical history (e.g. attacks associated with television viewing or with mounting an escalator). It is normally established by an EEG recording in which stroboscopic stimulation is associated with a "photoconvulsive response". This term describes the appearance of a generalized bilaterally symmetrical rhythmic discharge, either of classical spike and wave (at 3 Hz) or of polyspikes or polyspikes and waves.

The discharge is not time-locked to the photic stimulus (either in terms of its frequency or termination). It thus contrasts with the photomyoclonic response in which spikes and polyspikes occur symmetrically over the frontal-rolandic area, usually at a rate directly related to stimulus frequency and terminating with cessation of stimulation. In the photomyoclonic response, myoclonic jerking often involves the eyelids but may be more generalized, and is related to the rhythm of stimulation. This photomyoclonic response does not show a close relation to epilepsy. It is seen in a small percentage of normal subjects, but is most commonly found in psychiatric patients, particularly those with alcoholism (Kooi *et al.*, 1960; Small, 1971).

II. SYNDROME IN MAN AND BABOON: CLINICAL AND EEG COMPARISON

The photoconvulsive responses in man and baboons have in common a strong genetic element and show age and sex dependence. The familial

element in man has been emphasized by Doose and Gerken (1973). In baboons the maximal incidence is seen in an inbred subpopulation, and diminishes with outbreeding into the main population (Balzamo *et al.*, 1975). In man the incidence of photosensitive epilepsy is maximal in adolescence (the modal age for first referral is 12 years) with a male:female ratio of 2:3. A similar age and sex dependence is found in baboons (Balzamo *et al.*, 1975).

In man the frequency of stroboscopic stimulation that triggers photoconvulsive responses in the highest proportion of patients is about 20 Hz, although the range of effective frequencies may extend from a few flashes per second to frequencies as high as 60 Hz (Jeavons and Harding, 1975). In baboons the optimal frequency of flash stimulation is slightly higher (25–35 Hz; Fig. 1); the effective range is closely similar.

EEG recordings during photic stimulation reveal a marked difference between man and *Papio papio*. In the baboon paroxysmal activity (rhythmic polyspike and wave) commences symmetrically in the frontorolandic region, at a time when in the occipital region no pathological paroxysmal activities are identifiable (only normal visual evoked potentials and normal following). In contrast in man, characteristically, paroxysmal EEG discharges may be confined to the occipital and posterior temporal derivations either symmetrically or asymmetrically, or may appear nearly simultaneously over all head regions.

III. PHARMACOLOGIAL EVIDENCE: GABA AND DOPAMINE

In photosensitive baboons and in man there is now substantial pharmacological evidence suggesting that two neurotransmitter substances, 4-aminobutyric acid (GABA) and dopamine, have a powerful influence on photosensitive epilepsy.

A. Impairment of GABA-mediated inhibition

Convulsant drugs that antagonize the postsynaptic inhibitory effects of GABA, including bicuculline, picrotoxin and pentylenetetrazol, can facilitate the induction of the photoconvulsive response or photically induced seizures (Meldrum and Horton, 1971; Meldrum, 1979). These agents more potently block the postsynaptic depolarizing action of GABA, prominent in hippocampal pyramidal neurone dendrites, rather than the postsynaptic hyperpolarizing action of GABA, prominent at the level of the cell soma (Alger and Nicol, 1982). Compounds that block the synthesis of GABA, by inhibiting the enzyme glutamic acid decarboxylase, can enhance the natural

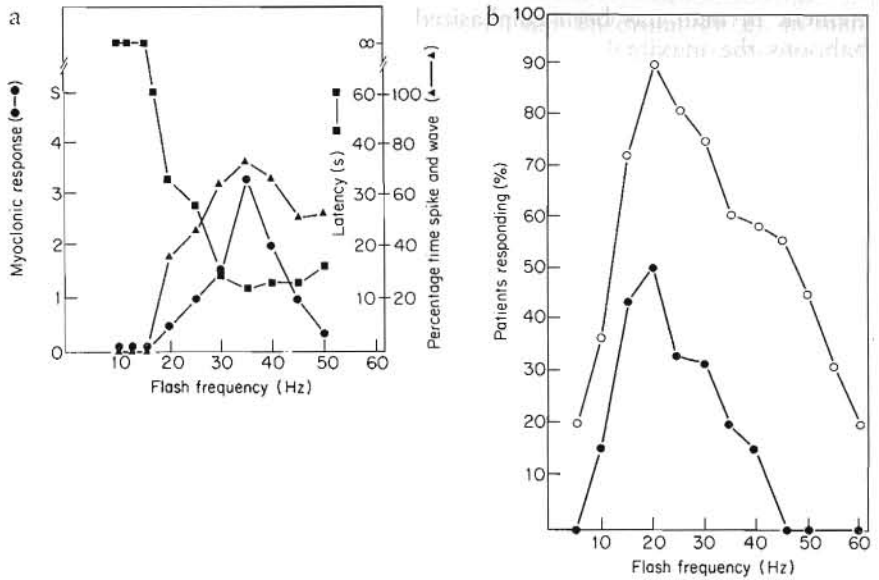

Fig. 1a "Tuning curves" showing the relationship between flash frequency and epileptic response in a highly photosensitive adolescent (post-menarche) female baboon. Points represent the mean of 2 or 3 60-s stimulation periods at each frequency, given in a random order. The graphs show the maximal myoclonic response (graded as 0 = none; 1 = myoclonus of eyelids; 2 = myoclonus of muscles of face and neck; 3 = myoclonus of trunk and all four limbs; 4 = myoclonus sustained beyond the end of photic stimulation; S = tonic–clonic seizure; intermediate values indicate more severe response occurred feebly or only transiently), the latency to fronto-rolandic spikes and waves (in seconds), and the percentage time showing spikes and waves on the EEG. (Data of A. J. Wilkins and B. S. Meldrum, reproduced from *Animal Models of Neurological Diseases* (1980) with permission.)

Fig. 1b Percentage of 52 photosensitive patients in whom a photoconvulsive response was obtained, expressed as a function of the flash frequency. O——O: responses obtained with open eyes; ●——●: responses obtained with closed eyelids. (Data from Jeavons and Harding (1975) p. 70, Fig. 26.)

syndrome of photosensitive epilepsy in baboons when given in doses substantially below the convulsant dose (Meldrum *et al.*, 1970; Horton and Meldrum, 1973; Meldrum *et al.*, 1975; Meldrum, 1979) without modifying any of the clinical or neurophysiological features. They also induce the syndrome in animals not originally showing photosensitive epileptic responses (Fig. 2a).

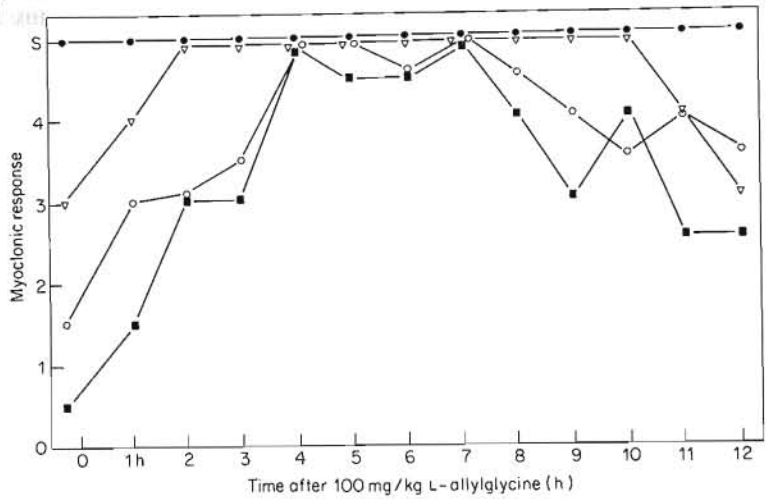

Fig. 2a Myoclonic or seizure responses to intermittent photic stimulation (25 Hz then 15–40 Hz) in 4 baboons of differing initial photosensitivity, before and at hourly intervals after receiving L-allyglycine 100 mg/kg i.v. The myoclonic responses are rated according to the scale in the legend to Figure 1*a* (an intermediate grade indicates that the higher response occurred feebly or only transiently). S = a full tonic–clonic seizure.

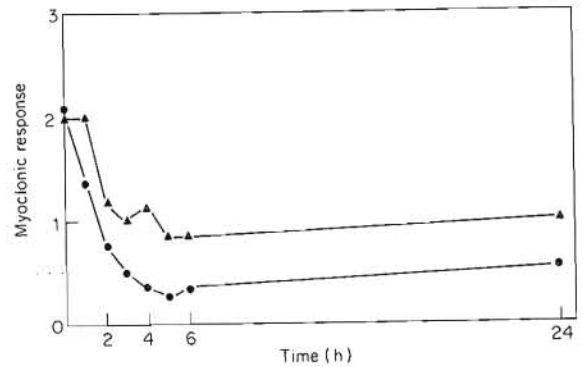

Fig. 2b Myoclonic responses to intermittent photic stimulation (25 Hz then 15–40 Hz) following the intravenous injection of (S)γ-vinyl GABA (100 ▲——▲ or 200 ●——● mg/kg) in the baboon *Papio papio*. Points represent the mean response (graded as in Fig. 1*a*) at each time after injection in 4 adolescent baboons.

Precisely comparable pharmacological studies are not available in man. However, photoconvulsive responses, photically induced myoclonus and seizures are all seen during withdrawal of barbiturates, benzodiazepines or alcohol, all conditions believed to be associated with a relative impairment of GABA-ergic inhibition.

B. Enhancement of GABA-mediated inhibition

Protection against photoconvulsive responses or photically induced seizures is obtained in man and the baboon by a number of drug treatments whose common feature is that they enhance GABA-mediated inhibition (i.e. benzodiazepines; barbiturates, GABA-transaminase inhibitors, such as vinyl GABA and sodium valproate; reviewed by Meldrum, 1979, 1982; Fig. 2b).

C. Dopamine agonists

Some compounds which mimic the action of dopamine (either at presynaptic receptors, decreasing dopamine release, or at postsynaptic receptors increasing cell firing) such as apomorphine, *n*-propylnoraporphine and various ergot derivatives, block photically induced myoclonus in *Papio papio* (Anlezark and Meldrum, 1978; Meldrum and Anlezark, 1981).

This effect is dependent on a central action of dopamine agonists as it is not blocked by prior administration of domperidone (which prevents "peripheral" effect of dopamine agonists, including nausea and emesis, but not central effects as it does not cross the "blood–brain barrier"). However, the site of anticonvulsant action of dopamine agonists within the brain is not yet defined, see Section VII).

In man photoconvulsive responses are abolished by the subcutaneous administration of low doses of apomorphine (Quesney *et al.*, 1980; Anlezark *et al.*, 1981).

IV. FUNCTION OF INTRACORTICAL GABA-ERGIC NEURONES

Immunocytochemical studies, using antibodies to the enzyme glutamic acid decarboxylase, have shown that in the rat visual cortex the aspinous and sparsely spinous stellate neurones are GABA-ergic (Ribak, 1978). Degeneration studies in the monkey cortex have shown that these neurones make synaptic contacts ("symmetrical") on the cell bodies of pyramidal neurones (Sloper and Powell, 1979). In layer IV of the cortex these stellate neurones are interconnected by gap junctions and appear to form a continuous horizontal

network. They are activated by collaterals of the cortical input and recurrent collaterals of the pyramidal neurone output (Fig. 3). Stellate neurones in the more superficial layers (II and III) appear to be grouped focally in a pattern corresponding to the ocular dominance columns (Hendrickson *et al.*, 1981).

It is likely that the horizontal net in the lamina 4 will exert a powerful inhibitory action spreading laterally when it is activated either by an excessively sustained cortical input or output, i.e. it should be brought into action either by appropriate intermittent or patterned visual inputs or by the early stage of a paroxysmal cortical discharge.

V. RESPONSES TO PATTERN SUGGEST A CORTICAL ORIGIN OF DISCHARGES

Studies of photoconvulsive responses to various patterns presented monocularly and binocularly and in different parts of the visual field (Wilkins *et al.*, 1979; 1980) indicate that the epileptogenicity of a pattern is determined at

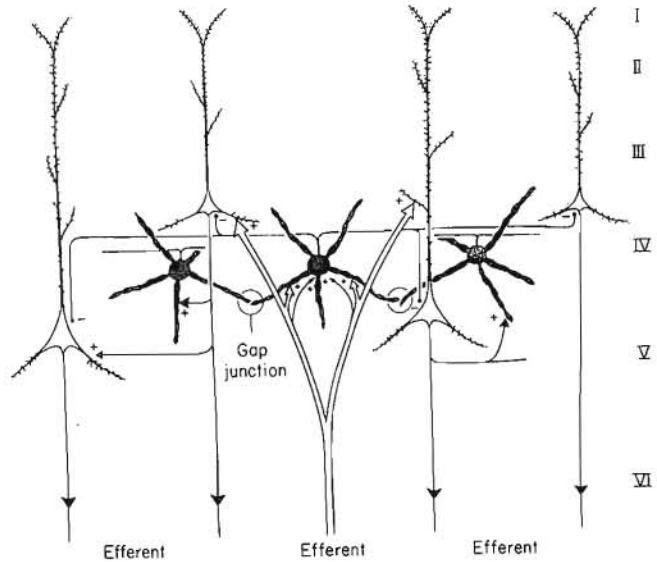

Fig. 3 Schematic diagram to show the pattern of termination of cortical afferent paths on large stellate neurones (black) and on pyramidal neurones, and relevant excitatory (+) and inhibitory (−) interconnections. Dendro-dendritic gap junctions are shown between the stellate neurones. Cortical laminae (I–VI) approximately indicated. (From Sloper and Powell, 1979, with permission.)

the cortical level. In particular, two lines of evidence – (1) that the linearity of contours is more significant than the total number (for example, the pattern of stripes shown schematically in Fig. 5c is more epileptogenic than the pattern of checks shown in Fig. 5d) and (2) that binocular rivalry between differently oriented line contours decreases the probability of paroxysmal activity – both point to an important role for events occurring in the visual cortex. This interpretation can be integrated with the pharmacological experiments mentioned above by considering the effects of a subconvulsive dose of bicuculline (0·2 mg/kg) on the properties of simple, complex and hypercomplex cells in the striate cortex of the cat (Pettigrew and Daniels, 1973). Receptive fields of some complex cells show a loss of specificity in relation to the orientation or direction of a moving line; hypercomplex cells lose their inhibitory end zones. The role of GABA-ergic lateral inhibition in defining the orientation specificity of complex cells has also been demonstrated using iontophoretic application of bicuculline (Sillito, 1979).

VI. A COMPREHENSIVE HYPOTHESIS: MINIMAL DIFFUSE GABA-ERGIC INSUFFICIENCY

The effect on photosensitive epilepsy in the baboon of drugs modifying GABA-ergic activity, considered in conjunction with the human data relating to patterns, and the special GABA-related properties of cells in the visual cortex, forces consideration of the hypothesis that the primary basis of photosensitive epilepsy is a minimal deficiency of the intracortical GABA-ergic system. This deficiency may be most severe in the occipital cortex or in the frontorolandic cortex, or it may involve the whole hemisphere diffusely. We make no assumption as to whether the functional deficiency arises from a biochemical abnormality (of enzymes, receptors or membranes) or an abnormality of the pattern of synaptic interconnections. Obviously if the number of GABA-ergic interneurones is reduced, then evidence may be found both for biochemical abnormalities (altered activity of glutamic acid decarboxylase, altered numbers of receptors sites) and for changes in synaptic patterns.

There is no direct evidence from biochemical or morphological studies for a deficiency of GABA-ergic inhibition in the cortex in photosensitive epilepsy, but there is evidence for a selective loss of GABA-ergic terminals in the vicinity of an epileptogenic focus created by alumina gel in the monkey sensorimotor cortex (Ribak *et al.*, 1979).

Experimental hypoxia in infant monkeys can lead to degeneration of cortical GABA-ergic terminals (Sloper *et al.*, 1980), but in the majority of patients (and indeed in the baboons) there is no evidence for a hypoxic episode in the perinatal period, or subsequently. The genetic data, and the age

and sex dependence of the photosensitive responses are nevertheless consistent with either a biochemical defect or a genetic abnormality expressed during development as a structural change. The enhancement of the phenomena in the adolescent female is consistent with the known effects of oestrogens on cerebral glutamic acid decarboxylase activity (Wallis and Luttge, 1980; McGinnis *et al.*, 1981).

VII. ROLE OF DOPAMINERGIC SYSTEMS

On the basis of a similar suppression of cortical spike activity after systemic and striatal injection of dopamine agonists in rats with cobalt-induced cortical foci, a striatal site of anticonvulsant action of dopamine has been proposed (Farjo and McQueen, 1979).

It has also been argued that there is an important role for the intracortical inhibitory action of the mesocortical dopaminergic system in photosensitive epilepsy (Reader *et al.*, 1976, 1979). This proposal arises from the demonstration that release of dopamine from the cat cortex is decreased by photic stimulation at 15 Hz. The physiological role of the nigrostriatal, mesolimbic and mesocortical dopaminergic systems remains to be defined. However, visual inputs do appear to increase metabolic activity in the basal ganglia as well as in occipital, temporal and prefrontal cortex (Macko *et al.*, 1982). The dopaminergic system is undoubtedly involved in the integration of movement with visual input, and this interaction is occurring partly at the level of the cortex and partly in the basal ganglia (Anderson *et al.*, 1979). At all levels (substantia nigra, striatum, cortex) there is a close relation to GABA-ergic inhibition. If a partial failure of GABA-ergic inhibition is induced by a subconvulsant dose of allylglycine in the baboon, apomorphine no longer blocks photically induced myoclonus but becomes proconvulsant.

VIII. EPILEPTIC NEURONES V. A MINIMAL EPILEPTIC AGGREGATE

The hypothesis of a diffuse partial failure of intracortical inhibition in photosensitive epilepsy is different from that proposed for focal epileptogenic lesions (Wyler and Ward, 1980). There is no need to postulate epileptic neurones that spontaneously show burst firing (as a result of intrinsic abnormalities) and then recruit "Group II" neurones into a similar pattern of synchronous firing. Instead burst firing can be seen as a property of a population of neurones which depends on the pattern of connectivity. A model of burst firing (in the hippocampus) that develops synchronization has

been described (Traub and Wong, 1982), but this does not incorporate features that are specifically relevant to the complex cell.

Studying foci induced in the visual cortex of the cat by the topical action of penicillin, Gabor and Scobey (1975) and Gabor *et al.* (1979) found that the focus could be defined in terms of columns of neurones with a common preferred axis of movement (for stimulation), i.e. the minimal unit in epileptogenesis appeared to be a number of cells with the same preferred axis of movement, and ocular dominance, for a single retinal field site.

IX. FRONTOROLANDIC RESPONSES IN *PAPIO PAPIO*

Paroxysmal discharges during photic stimulation in the baboon originate in a region of the frontorolandic cortex that appears to receive multiple afferent inputs conveying visual information, information relating to eye movement, and information from periorbital tissues (Menini, 1976). That afferents other than those conveying visual information are important in epileptogenesis is shown by the absence of paroxysmal responses in the curarized baboon (Fischer-Williams *et al.*, 1968) and the protective effect of periorbital local anaesthesia (Naquet and Manini, 1972). By analogy with the special involvement of columns of cells in the occipital cortex, it may be suggested that homologous columns of cells representing a level of analysis that involves integration of somatosensory and visual information, play a special role in epileptogenesis in the baboon. The induction in photosensitive patients of seizures associated with slow eye closure plus upward rotation of the eyeballs (Darby *et al.*, 1980) suggests that similarly convergent inputs may contribute to epileptogenesis in man although the eye movement may not be the initial event in the seizure induction (Wastell *et al.*, 1982). (We have observed that *Papio papio* make a similar slow closure of the eye, but the association between this movement and the occurrence of paroxysmal activity has yet to be studied.) There is also evidence from somatosensory evoked potentials in patients with photosensitive epilepsy that there is a functional abnormality in the somatosensory cortex (Broughton *et al.*, 1969).

Recording of single cell cortical unit activity is technically possible in the ventilated, peripherally paralysed baboon, in which paroxysmal discharges cannot normally be induced by photic stimulation. After pretreatment with a subconvulsive dose of allylglycine – which reduces the synthesis of GABA by inhibiting the activity of glutamic acid decarboxylase (Horton and Meldrum, 1973) – intermittent flashes induce paroxysmal discharges in the frontorolandic and not the visual cortex. These are associated with typical epileptic burst discharges in units in the frontal cortex, but no burst discharges in the occipital or parietal cortex (Menini *et al.*, 1981).

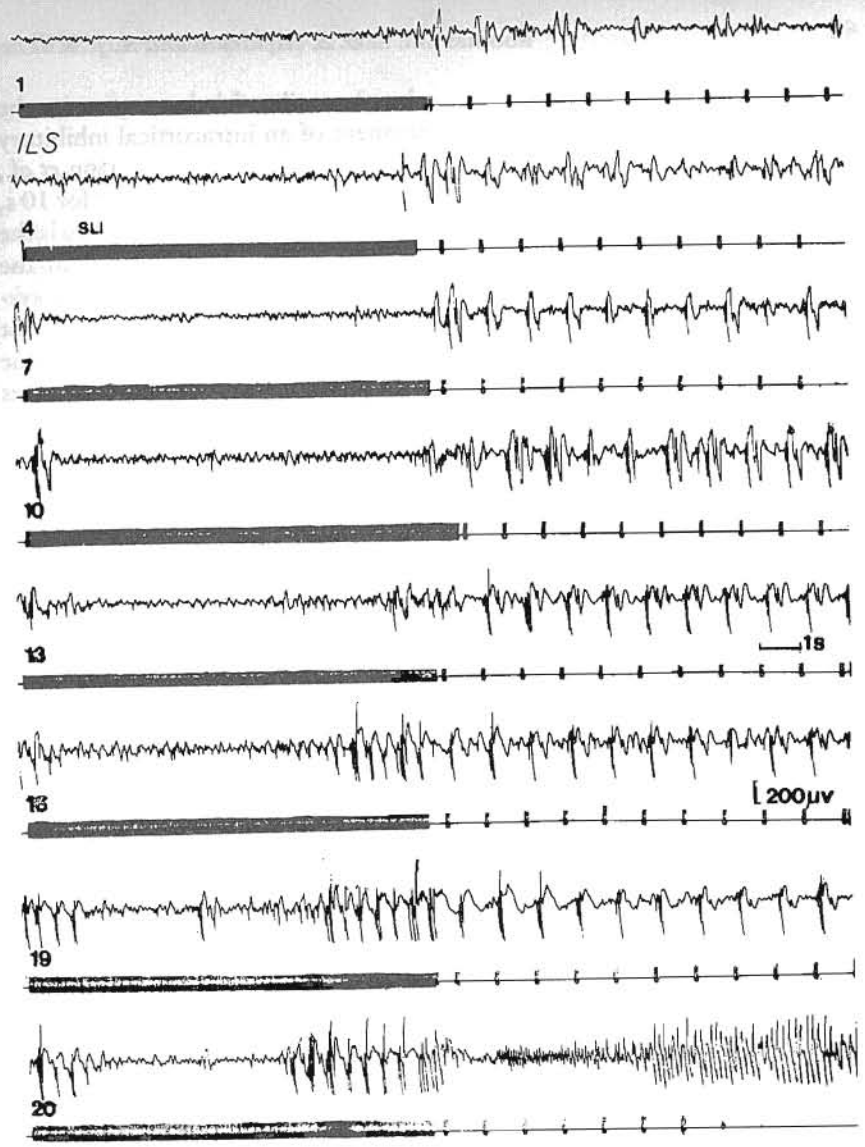

Fig. 4 Electrocorticographic recording (upper channel) from the frontal cortex in a baboon paralysed with flaxedil, mechanically ventilated, and pretreated with allylglycine 150 mg/kg i.v. Lower channel indicates flash stimulation given in blocks at 25 Hz for 10 s then in triplets every 1 s for 10 s. Number 1, 4, 7, etc refer to sequential blocks of 10 s stimulation. Paroxysmal discharges evoked by sustained 25 Hz flash are rarer than in the non-paralysed animal. However, paroxysmal visual evoked potentials occur with increasing frequency and regularity during the sequence of stimulation. A generalized seizure occurred after the 20th sequence. (From Stutzmann, Laurent, Valin and Menini, 1980, with permission.)

The use of allylglycine in the paralysed ventilated baboon permits the demonstration of the cumulative impairment of an intracortical inhibitory process during the course of rhythmic photic stimulation (Stutzmann *et al.*, 1980). Following multiple exposures to flash stimulation (at 25 Hz) for 10 s, with 10-s intervals during which single or triple flashes are given, there is the progressive development of paroxysmal visual evoked potentials in the frontorolandic cortex. Their appearance precedes that of the usual paroxysmal discharges induced by the 25-Hz flash stimulation (Fig. 4). Single unit burst-firing occurs with the same pattern and involves units at the same cortical depth in paroxysmal evoked potentials and in paroxysmal discharges (Silva-Comte *et al.*, 1982).

X. FAILURE OF AN INHIBITORY SYSTEM UNDER OVERLOAD

The neurophysiological data from baboons, either with somatosensory input and no allylglycine or with allylglycine but no somatosensory input, and the data from patterns in man can all be interpreted in terms of failure of an inhibitory network, such as the GABA-ergic intracortical system, under a condition of overload. Consideration of the pathophysiology of synaptic systems suggests several possible mechanisms for such failure. One that has been described in the hippocampus is "desensitization" of the GABA receptor system (Ben-Ari and Krnjević, 1981). With certain frequencies of stimulation the postsynaptic cells become desensitized to the inhibitory effect of GABA (released synaptically or from a micropipette). The experiments with allylglycine would appear to exclude such a mechanism, at least for the frontorolandic cortex, as a decreased rate of GABA synthesis would have a protective effect if desensitization were important. However two possible mechanisms remain for consideration. One is "occlusion" of inhibitory inputs, the other an insufficient maximal rate of synthesis of GABA. The former implies that each excitatory input to the complex cells in the visual cortex (or their homologues in the frontorolandic cortex) is matched by a collaterally activated inhibitory input, but that several inputs share the same inhibitory system so that the balance of excitation and inhibition is not maintained under certain patterns of simultaneous excitatory input (see Section XIV). The alternative is that, with particular inputs, activity is so sustained within certain elements in the GABA-ergic system that the rate of synaptic release of GABA appropriate to the activity exceeds the maximal rate of synthesis (and reuptake) of GABA.

XI. EXCESS EXCITATION V. DIMINISHED INHIBITION

Although it may not always be meaningful to differentiate between excess excitation and diminished inhibition in a system whose activity is controlled by negative feedback, there are some pathological or pharmacological circumstances where this distinction may be useful.

The recent development of potent and selective antagonists of excitation due to dicarboxylic amino acids (Watkins and Evans, 1981) has provided tools for examining the role of specific neurotransmitters (or receptors) in the spread of excitation during seizure activity. In particular, compounds that block excitation produced by 2-amino-7-phosphono-heptanoic acid prevent sound-induced seizures and some, but not all, classes of chemically-induced seizures (Croucher *et al.*, 1982; Czuczwar and Meldrum, 1982). Furthermore Meldrum *et al.* (1983a) have shown that 2-amino-7-phosphono-heptanoic acid will block photically induced myoclonus in *Papio papio*. Although the endogenous transmitter substance acting at sites preferentially activated by *N*-methyl-*D*-aspartate is not definitely known, aspartic acid is the most probable endogenous agent. There is some evidence that 2-amino-7-phosphono-heptanoic acid is relatively more active against aspartate than against glutamate (Roberts *et al.*, 1982; Meldrum *et al.*, 1983).

There is no evidence that cortical excitatory transmission is abnormal or enhanced in photosensitive epilepsy in man or the baboon. Studies employing systemically administered penicillin in the cat have been interpreted as showing that generalized spike and wave discharges correlate with enhanced sensitivity of cortical neurones to excitatory inputs from the thalamus, rather than with impaired recurrent inhibition within the cortex (Avoli and Gloor, 1982; Kostopoulos *et al.*, 1982). The relevance of these observations to photically induced epilepsy is uncertain. It is possible to induce paroxysmal discharges by photic stimulation in the penicillin-treated cat (Quesney, 1981), but massive doses of penicillin given intravenously in *Papio papio* have no effect on seizure threshold.

XII. CRITICAL MASS

If a minimal inhibitory failure is responsible for photosensitivity (as outlined in Section X), there may be a "critical mass" of excitation below which no paroxysmal discharge occurs and above which a discharge is likely. If the failure of inhibition is diffuse it should not matter in which part of the

network the discharge is initiated; the cortex might be said to be "equipotential".

Wilkins *et al.* (1980) have produced evidence that in human photosensitive patients paroxysmal EEG discharges occur once the normal physiological excitation that results from pattern stimulation exceeds a critical amount. Their evidence is based on the fact that photosensitive patients generally show no impairment of visual function interictally (see also Soso *et al.*, 1980). Visual stimulation may therefore induce normal physiological excitation, at least interictally. When photosensitive patients look at certain patterns of stripes with appropriate spatial properties epileptiform paroxysmal EEG abnormalities are induced, and, when focal, their topography is quite consistent with that of a discharge confined to striate and prestriate areas (see Section XIII).

The probability of these abnormalities occurring is critically dependent on the size of the pattern. For centrally fixated patterns of stripes, circular in outline (Fig. 5e, f), there appears to be a critical pattern radius, differing from patient to patient, below which no paroxysmal activity appears and above which the probability of paroxysmal activity increases with the logarithm of pattern radius. For patterns comprising sectors of concentric rings (Fig. 5g, h) the probability of paroxysmal activity is similar when the patterns have the same total area, that is when $\alpha = 2\beta$. Since the two patterns (Fig. 5g and 5h) stimulate different regions of the visual cortex the hyperexcitability within the visual cortex of each hemisphere is evidently diffuse. When the central section of a pattern of vertical stripes is removed, so as to form a striped annulus (Fig. 5i), the probability of paroxysmal activity decreases by an amount that may be predicted from estimates of the human cortical magnification factor (Wilkins *et al.*, 1980). Evidently there is a critical mass of cortical excitation necessary for epileptogenesis, and the cortex is partially equipotential in this regard, at least within each hemisphere.

These observations parallel those of Gabor and Scobey (1975) who have used penicillin iontophoresis in the visual cortex of the cat. They find that there is a critical level of visual stimulation, expressed in terms of the size of a flashing spot, below which no paroxysmal discharge occurs, and above which the probability of a discharge increases with spot size. The critical size of the flashing spot necessary to induce paroxysmal activity varies with retinal eccentricity in such a way as to suggest that the number of cells excited by the spot determines the threshold for a discharge (however, see discussion by McIlwain, 1976).

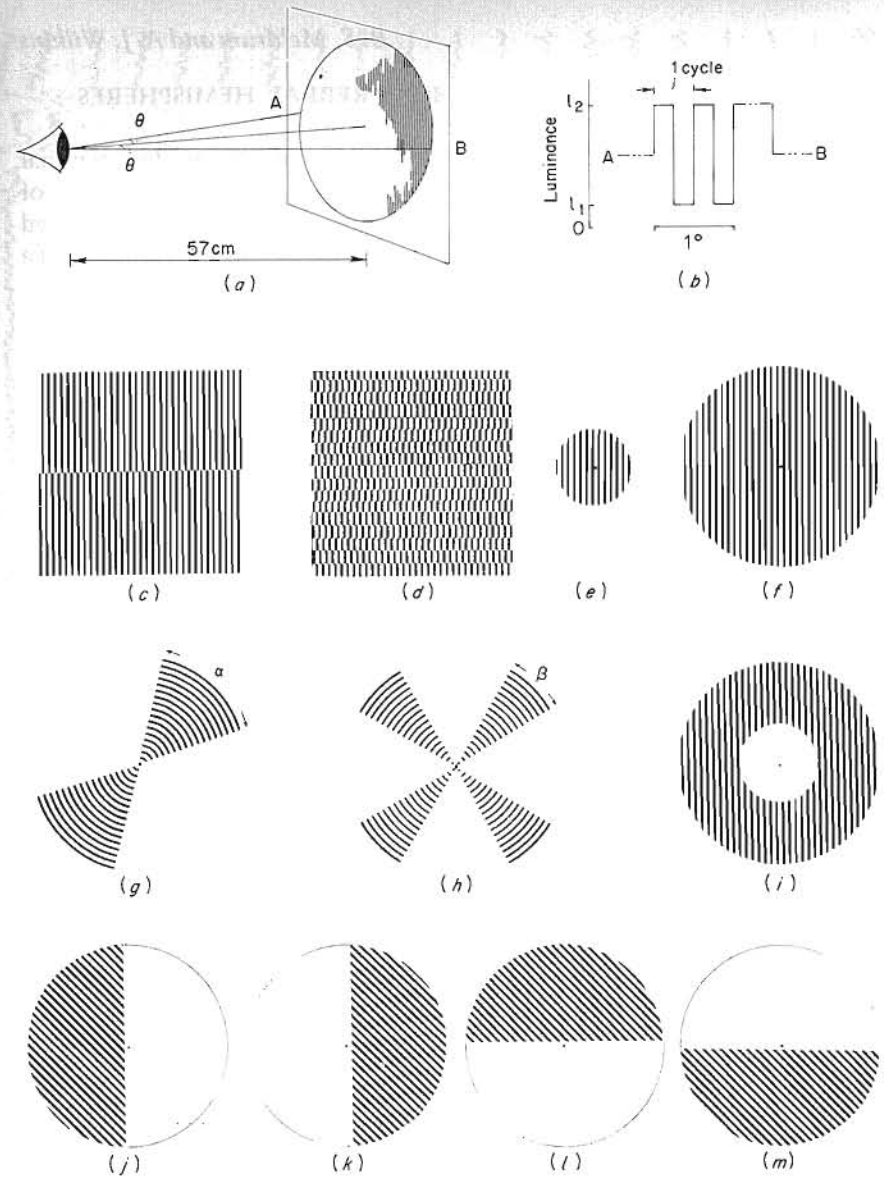

Fig. 5 Parameters of pattern stimulation shown (*a*) in three-quarter view and (*b*) by luminance profile. (*c*)–(*m*) Schematics of individual patterns, showing the central fixation point. The patterns were viewed binocularly. They were printed on card and held against a screen lit by steady diffuse white light. Typical pattern parameters were as shown in (*b*): spatial frequency 2 cycles/degree; contrast $[(l_2 - l_1)/(l_2 + l_1)] = 0{\cdot}7$; mean luminance $[(l_2 + l_1)/2] \approx 300$ cd/m^2. The angular radius (θ) of patterns *e*, *f*, *i*, *j*, *k*, *l* and *m*, was adjusted to suit the sensitivity of the individual patient and ranged from 3°–24°. For patterns *g* and *h* the sector angles α and β were adjusted.

XIII. INDEPENDENCE OF THE CEREBRAL HEMISPHERES

Wilkins *et al.* (1981) found that stimulation, by pattern, of one lateral visual hemifield (Fig. 5j, k) was usually more epileptogenic than stimulation of either the upper or lower hemifield, (Fig. 5l, m) although the pattern involved was similar. This finding may be explained on the basis that the *initiation* of a discharge can be independent in the two cerebral hemispheres. When the upper visual field is stimulated bilaterally, the excitatory input received by either hemisphere is less than that received by one hemisphere alone when the appropriate lateral hemifield is stimulated.

The EEG disturbances induced by patterns are often confined to post-central derivations, and when a lateral field is stimulated the response is usually seen over the contralateral hemisphere (Fig. 6a, b). When the upper field is stimulated the response, when it occurs, is usually bilateral (Fig. 6 c, d). These findings are quite consistent with the independent initiation of a discharge in the two hemispheres.

Responses are often far more readily induced from one lateral field than the other (Wilkins *et al.*, 1981). This difference between the visual fields is therefore not only consistent with the induction of a discharge confined to one hemisphere, it also suggests that the visual cortex of the two cerebral hemispheres may have a different photoconvulsive threshold. Evidence for a difference in the hyperexcitability of the hemispheres is obtained not only for patients with partial and secondary generalized epilepsy but also those with primary generalized epilepsy who are supposed to suffer a diffuse cortical hyperexcitability (Binnie *et al.*, 1981). The failure of inhibitory mechanisms in the two hemispheres may not therefore be as uniform as has previously been postulated in the model of generalized epilepsy proposed by Gloor (1979).

XIV. BURSTING AND THE PAROXYSMAL DEPOLARIZATION SHIFT

Calvin (1975, 1978) has reviewed evidence that when multiple excitatory inputs co-occur, pyramidal neurones in the cortex or hippocampus show a paroxysmal depolarization shift associated with a sterotyped burst of high frequency firing. In any highly interconnected neural network the probability of temporally coincident excitatory input to a given cell might be expected to increase not only with the number of neurones excited but also the rate at which they are caused to fire. In studies of the visual cortex of the

Fig. 6 Examples of the paroxysmal EEG activity recorded during the presentation of a pattern in (*a*) the left, (*b*) the right, (*c*) the upper and (*d*) the lower visual field. Recordings are from one patient.

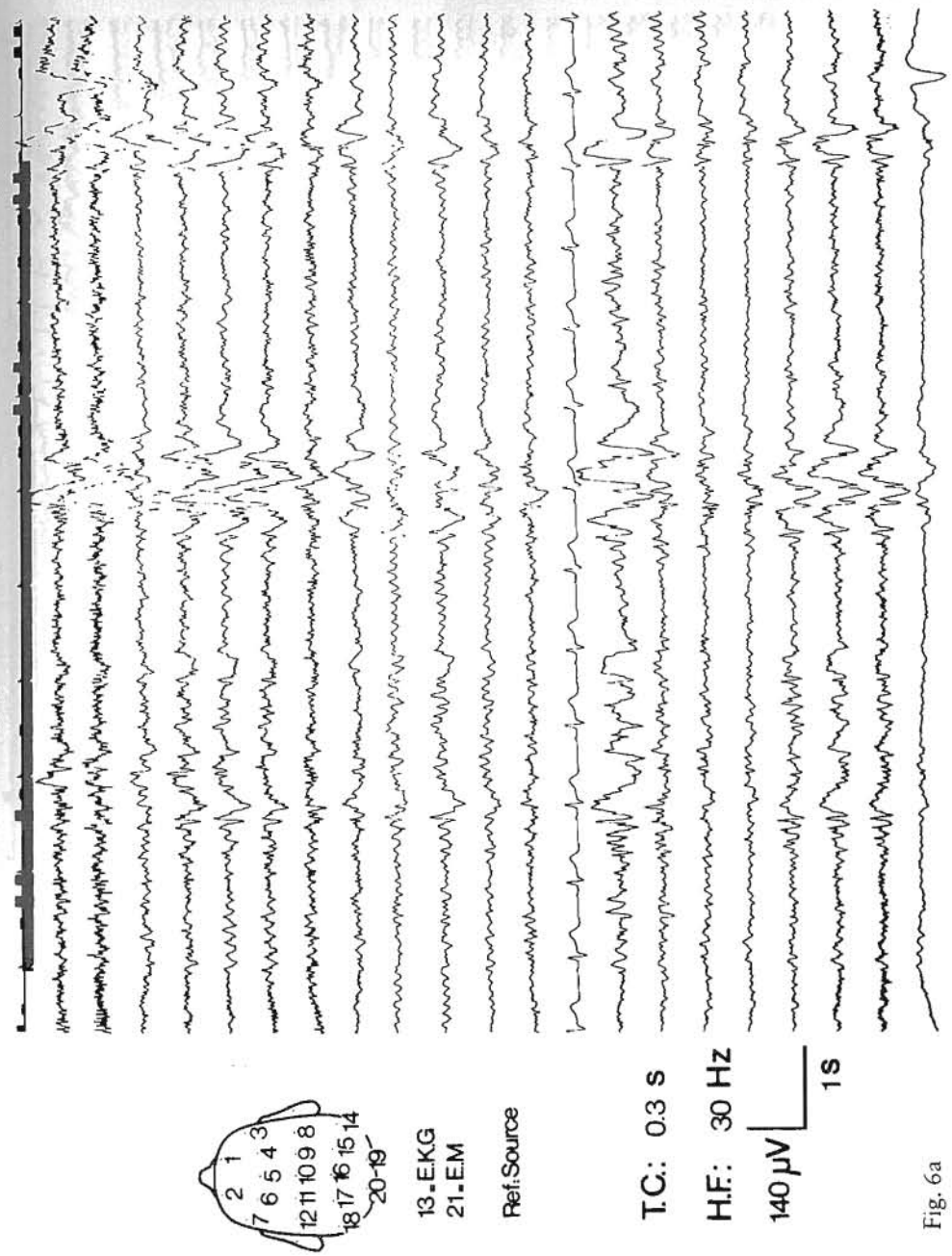

Fig. 6a

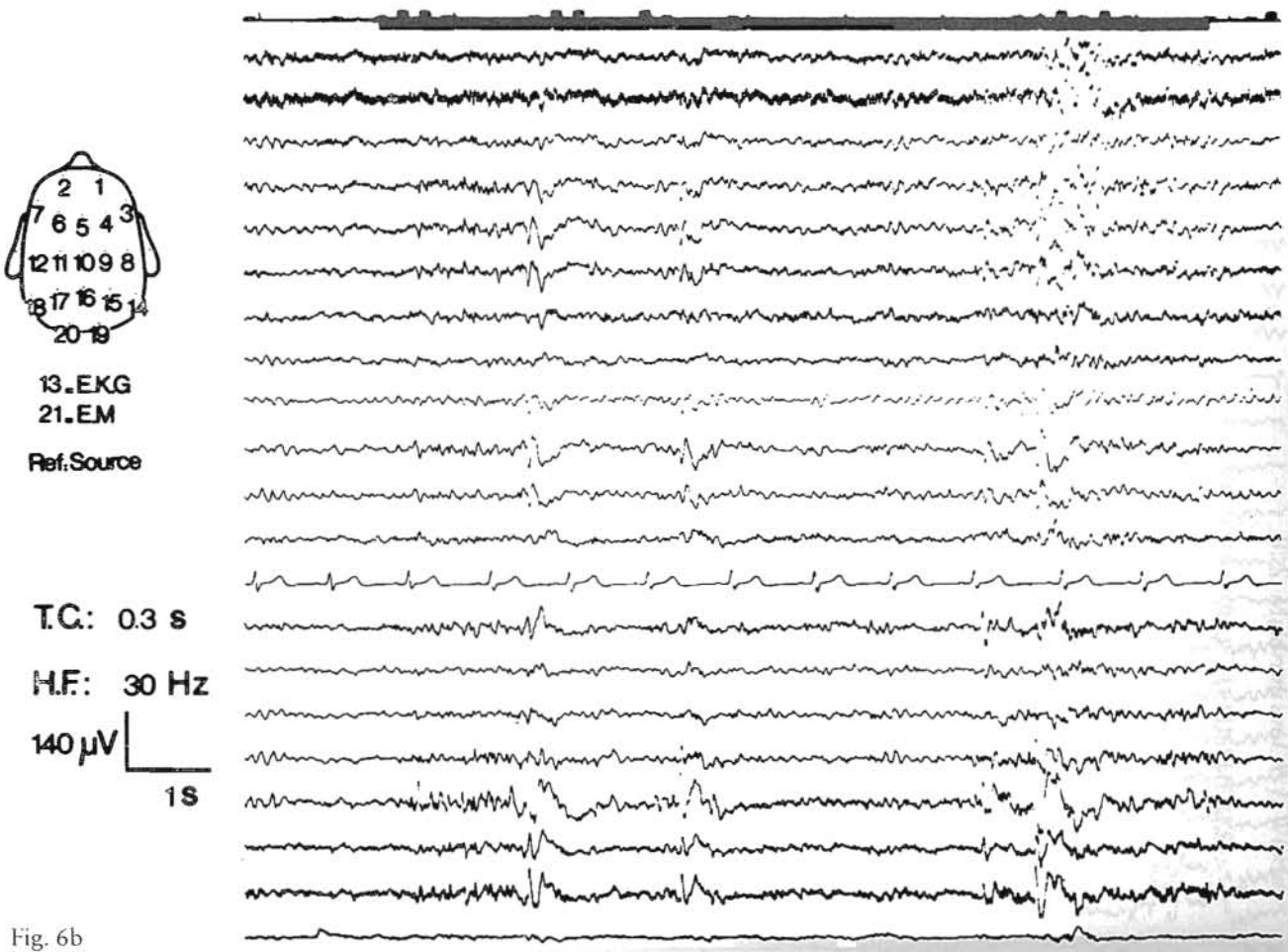
2 1
7 6 5 4 3
12 11 10 9 8
18 17 16 15 14
20 19
13. EKG
21. EM
Ref. Source
T.C.: 0.3 s
H.F.: 30 Hz
140 µV
1 s

Fig. 6b

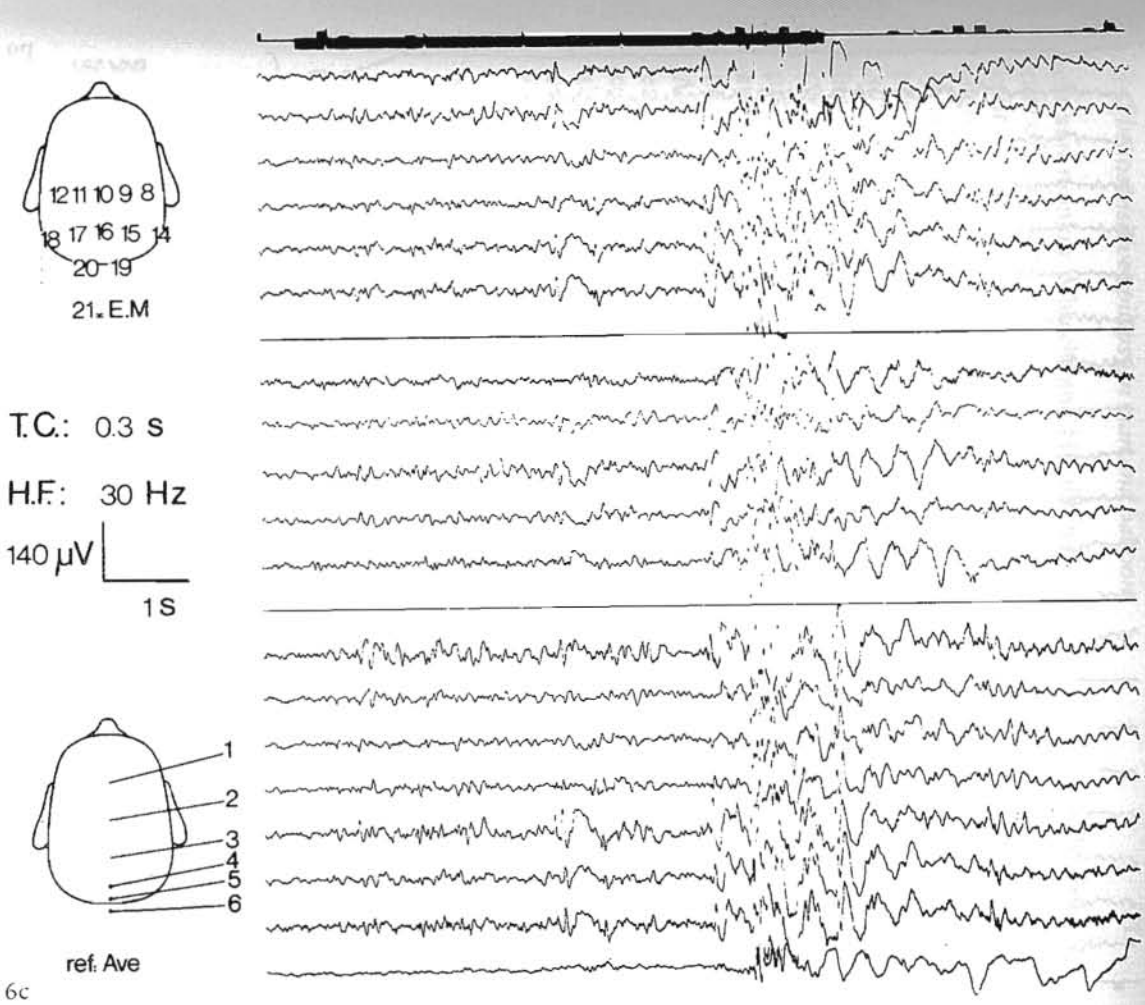
12 11 10 9 8
18 17 16 15 14
20 19
21. E.M
T.C.: 0.3 s
H.F.: 30 Hz
140 µV
1 s
1
2
3
4
5
6
ref. Ave

Fig. 6c

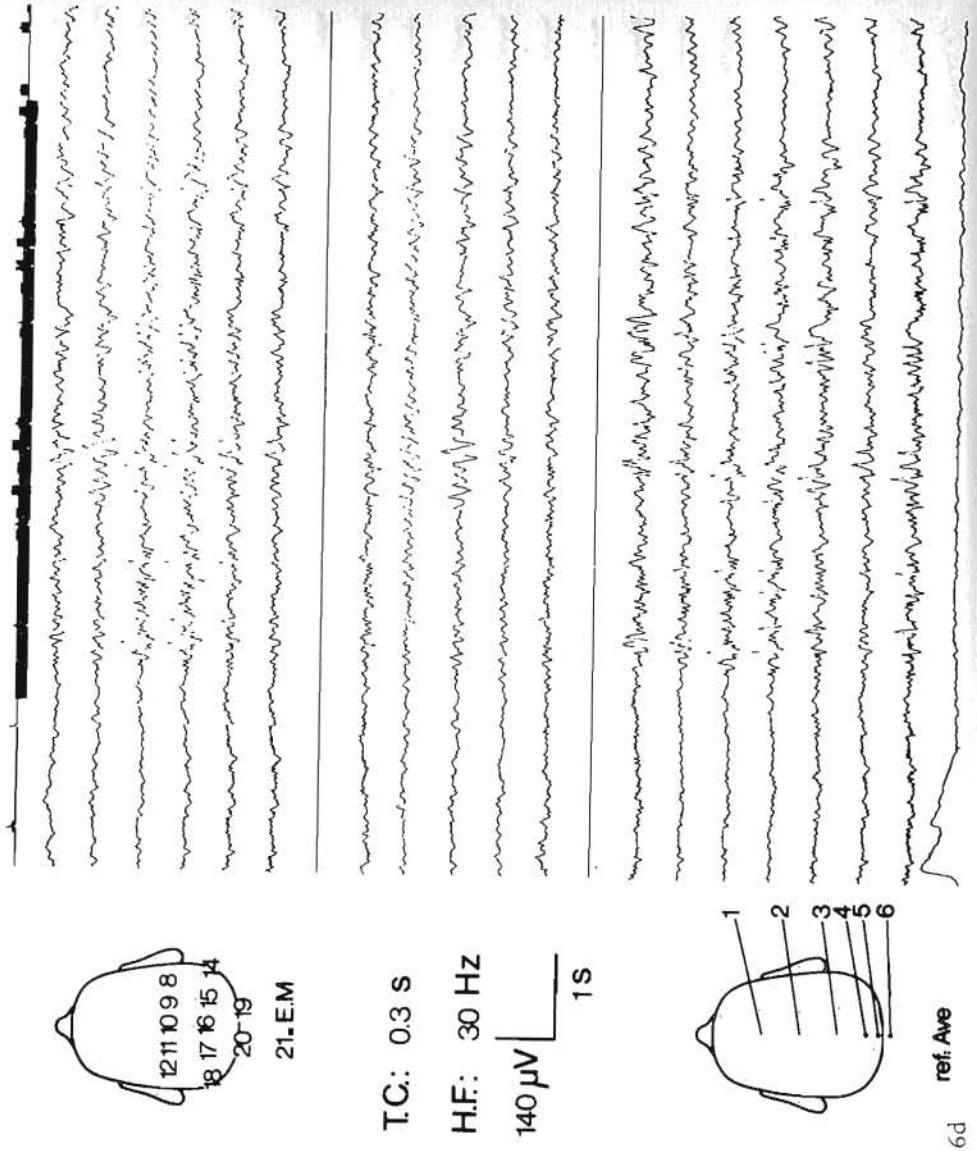

Fig. 6d

cat and monkey Albrecht and Hamilton (1982) have shown that the firing rate of a cell depends on the contrast across the receptive field of that cell. At contrasts greater than 30%, most cells have saturated or begun to do so. It is therefore of interest that the probability of paroxysmal epileptiform activity in response to visual patterns depends critically on the contrast of those patterns (see legend for Fig. 5). As the contrast is increased between 5 and 30%, the incidence of paroxysmal activity increases precipitously but with increases above 30% there is little or no further increase in the incidence (Wilkins *et al.*, 1980). The "plateau" above 30% in the function relating the probability of paroxysmal activity to contrast may therefore be taken as evidence suggesting that the critical mass of excitation, referred to above, is best expressed not only in terms of the units excited, but also their firing rate. As previously mentioned, these parameters of excitatory input might be expected to affect the probability of temporally coincident excitatory input to cells within a network. If the excitation were extreme, and in particular if there were some failure of inhibitory mechanisms, some neurones might be expected to burst in the fashion typical of those in epileptic foci. Menini *et al.* (1981) have shown that in the frontorolandic cortex of *Papio papio* injected with a subconvulsant dose of allylglycine the reactivity of cells to photic stimulation is similar to that observed in cortical epileptogenic lesions in man and animals, even though the cortex is not injured and shows no spontaneous paroxysmal activity.

XV. THE ROLE OF SYNCHRONY

According to the above conception, synchronization within the network is not a necessary precursor for the appearance of epileptiform activity. It is only necessary that individual neurones within the network receive multiple excitatory inputs within the brief period of time that the cell can "integrate" its input. The synchronous firing of neurones in the network may, however, result when the number of bursting neurones has reached the point at which they mutually excite one another. Some support for this viewpoint can be derived from the work of Menini *et al.* (1981), who showed a progressively stereotypical firing of neurones as firing rate increased. Synchrony may therefore be the *end result* of a massive excitatory input that is temporally disorganized, at least initially. Some preliminary experiments by one of the authors provide limited evidence for this view. Many visual neurones are sensitive to contours in their receptive field only when the contours drift in one direction, and the directional selectivity varies from cell to cell. Patterns of stripes that vibrate might therefore be expected not only to excite cells by virtue of the movement of the contours but to cause that excitation to occur

intermittently, mainly when the image of the stimulus on the retina is in motion. Patterns of stripes that drift continuously in one direction should cause no such temporal intermittency because of the overlap of receptive fields. In other words drifting patterns should not produce synchronous excitation. Preliminary studies with photosensitive patients have compared static and vibrating gratings with those that drift. (The drifting gratings were divided into left and right halves, each drifting towards a central fixation point: nystagmus was thus avoided.) The vibrating and static gratings were more epileptogenic than the drifting gratings, but the latter did occasionally induce epileptiform EEG activity. This is of interest because although it is impossible to know which of these stimuli induced the greatest excitation, it is fair to assume that any excitation induced by the drifting grating was temporally disorganized.

If synchronization of induced excitation is not strictly necessary for epileptogenesis, it is perhaps too easy to assume that because a flash of light may synchronize the neurones it excites, this synchronization is the reason for the epileptogenic properties of a train of flashes. Given the time course of recurrent inhibition, flashes of a given frequency may simply be an efficient means of maximizing excitatory input to the visual system. That input is unlikely to be maximized in the cortex, however. The highest temporal frequency at which cortical units will respond is far lower than that for units in the lateral geniculate nucleus of the thalamus, and in the cat and monkey is about 20 Hz, lower than the maximum epileptogenic frequencies in man or *Papio papio* (J. G. Robson, personal communication).

XVI. SPECULATIONS REGARDING THE SPATIAL DISTRIBUTION OF EXCITATION

The induction of an epileptic discharge may not depend simply on the extent of induced excitation. The distribution of this excitation within the network may also be important. Patterns of stripes will stimulate only cells that have the appropriate orientation and spatial frequency selectivities, and cells with these selectivities occur in columns that are widely distributed within the cortex, in a pattern that may itself be striped (Hubel and Wiesel, 1977; Tootell *et al.*, 1981). Striped visual patterns may therefore stimulate not a spatial concentration of cortical units but a widely distributed pattern of firing that may serve to enhance the epileptogenic properties of the excitation that results. Each excited column will presumably be surrounded by inhibition that makes demands on the local availability of an inhibitory neurotransmitter. If the spacing of excitation is such that the fields of surrounding inhibition overlap, "occlusion" may occur, or the synthesis and reuptake of

neurotransmitter within these fields may be unable to meet demand (see Section X).

XVII. GRADIENT OF EPILEPTOGENESIS

Gloor (1979) has argued that there exists a gradient of epileptogenesis, the mild end of which is reflected in spike and wave EEG discharges, and the severe in discharges of the focal type. The dissociation was originally phrased in terms of the presence or absence of paroxysmal depolarization, but this depolarization has now been described in the reversible generalized epilepsy of the *Papio papio* treated with allylglycine, a preparation that exhibits a spike and wave discharge (Menini *et al.*, 1981). If the paroxysmal depolarization shift is seen not as a reflection of damaged neurones but simply as the response to excessive excitation (see Section X), it is easy to see how a progressive failure of inhibition might lead to a progressively increasing incidence of paroxysmal depolarization. The presence of paroxysmal depolarization would depend on the firing rate within the neural network as a whole, and this in turn would reflect excitatory cortical input. If this input were *massive* and *distributed*, as is the case with thalamocortical input and with certain forms of visual stimulation, the excitation might well be sufficient for paroxysmal depolarization. According to this conception, the gradient of epileptogenesis has generalized epilepsy at its milder end because it occurs when the inhibitory failure is not extreme. When it is not extreme, only massive afferent volleys are sufficient to initiate the discharge. These are more likely to be widespread than focal, and the resulting discharge is therefore more likely to be generalized.

Both acute and chronic studies have shown that valproate can eliminate the photoconvulsive EEG response in humans (Harding *et al.*, 1978; Rowan *et al.*, 1979). Sometimes the response is not eliminated but the degree of generalization reduced, so that paroxysmal activity is seen only in posterior head regions (Binnie *et al.*, 1980). In a recent study of the effects of sodium valproate on pattern sensitivity, Park *et al.* (1982) found that the probability of a paroxysmal discharge was reduced, and when such a discharge did occur it was less generalized. However, the size of a pattern just sufficient to induce the response showed relatively little change with increasing valproate dose. This finding supports the idea that valproate affects the spread of epileptic disturbance but not the physiological activation necessary for its initiation. (The decrease in the probability of observing paroxysmal activity on the scalp EEG can be attributed to the reduced spread of epileptic activity.)

The excitation that initiates epileptiform activity need not be sensory nor the result of thalmic stimulation. There is every reason to suppose that the

localized excitation that subserves cognitive processes may on occasions be sufficient to induce paroxysmal activity (Wilkins *et al.*, 1982).

On the above basis it is possible to explain the coexistence in the same patient of focal and generalized EEG features. Wilkins *et al.* (1981) have demonstrated that in patients with *generalized* epilepsy, focal or generalized spike or spike and slow wave abnormalities can be induced by visual stimulation, and that when focal their topography is appropriate to the region of visual cortex stimulated (see Fig. 6). Whether the discharge is focal therefore depends in part on the induced excitation as well as on the underlying pathology. The localization of an epileptic discharge should perhaps be seen as reflecting an interaction between more or less regional inhibitory failure and more or less localized excitation that need not be pathological but can be the result of normal sensory and cognitive processes.

XVIII. CONCLUSION

In this chapter we have argued that there exists a critical level of normal neural excitation necessary for epileptogenesis and that the cortex may be partially equipotential with respect to the site and extent of excitation necessary. We have argued that the temporal organization of epileptic disturbance (the bursting and ultimate synchrony) are reflections of properties of the neural net as much as the component neurones. These are verbal descriptions of properties of a model that has received an elegant mathematical expression in the work of Anninos and Cyrulnik (1977).

An intracortical GABA-ergic inhibitory system plays a major role in determining the properties of visual neurones, and pharmacological manipulation of this system modifies photically induced epileptic responses. The biochemical and anatomical pathology underlying photic epilepsy remains to be demonstrated.

REFERENCES

Albrecht, D. G. and Hamilton, D. B. (1982). *J. Neurophysiol.* **48**, 217–237.

Alger, B. E. and Nicholl, R. A. (1981). *J. Physiol. (London)* **328**, 125–141.

Anderson, R. J., Aldridge, J. W. and Murphy, J. T. (1979). *Brain Res.* **173**, 489–501.

Anlezark, G. and Meldrum, B. (1978). *Psychopharmacology* **57**, 57–62.

Anlezark, G., Marrosu, F. and Meldrum, B. (1981). *In* "Neurotranmitters, Seizures and Epilepsy" (P. L. Morselli, K. G. Lloyd, W. Löscher, B. Meldrum, E. H. Reynolds, ed.), pp. 263–274. Raven Press, New York.

Anninos, P. A. and Cyrulnik, R. A. (1977). *J. Theor. Biol.* **66**, 695–709.

Avoli, M. and Gloor, P. (1982). *Exp. Neurol.* **76**, 196–217.

Balzamo, E., Bert, J., Menini, Ch. and Naquet, R. (1975). *Epilepsia* **16**, 269–276.

Ben-Ari, Y. and Krnjević, K. (1981). *In* "Neurotransmitters, Seizures and Epilepsy" (P. L. Morselli, K. G. Lloyd, W. Löscher, B. Meldrum and E. H. Reynolds, ed.), pp. 63–73. Raven Press, New York.

Binnie, C. D., de Korte, R. A., Meijer, J. W. A., Rowan, A. J. and Warfield, C. (1980). *Roy. Soc. Med. int. Congress* and Symposium No. 30. Academic Press, London.

Binnie, C. D., Wilkins, A. J. and De Korte, R. A. (1981). *Electroenceph. clin. Neurophysiol.* **52**, 469–472.

Broughton, R., Meier-Ewert, K.-H. and Ebe, M. (1969). *Electroenceph. clin. Neurophysiol.* **27**, 375–386.

Calvin, W. H. (1975). *Brain Res. (Amsterdam)* **84**, 1–22.

Calvin, W. H. (1978). *In* "Abnormal Neuronal Discharges" (N. Chalazonitis and M. Boisson, ed.). Raven Press, New York.

Croucher, M. J., Collins, J. F. and Meldrum, B. S. (1982). *Science* **216**, 899–901.

Czuczwar, S. J. and Meldrum, B. (1982). *Europ. J. Pharmacol.* **83**, 335–338.

Darby, C. E., De Korte, R. A., Binnie, C. D. and Wilkins, A. J. (1980). *Epilepsia* **21**, 31–42.

Doose, H. and Gerken, H. (1973). *Neuropädiatrie* **4**, 162–171.

Farjo, I. B. and McQueen, J. K. (1979). *Brit. J. Pharmacol.* **67**, 353–360.

Fischer-Williams, M., Poncet, M. and Naquet, R. (1968). *Electroenceph. clin. Neurophysiol.* **25**, 557–569.

Gabor, A. J. and Scobey, R. P. (1975). *J. Neurophysiol.* **38**, 395–404.

Gabor, A. J., Scobey, R. P. and Wehrli, C. J. (1979). *J. Neurophysiol.* **42**, 1609–1625.

Gloor, P. (1979). *Epilepsia* **20**, 571–588.

Harding, G. F. A., Herrick, C. E. and Jeavons, P. M. (1978). *Epilepsia* **19**, 555–565.

Hendrickson, A. E., Hunt, S. P. and Wu, J.-Y. (1981). *Nature* **292**, 605–607.

Horton, R. W. and Meldrum, B. S. (1975). *Brit. J. Pharmacol.* **49**, 52–63.

Hubel, D. H. and Wiesel, T. N. (1977). *Proc. Roy. Soc.* **198B**, 1–59.

Jeavons, P. M. and Harding, G. F. A. (1975). "Photosensitive Epilepsy. A Review of the Literature and a Study of 460 Patients." Heinemann Medical, London.

Kooi, K., Thomas, M. H. and Mortenson, F. N. (1960). *Neurology (Minneap.)* **10**, 1051–1058.

Kostopoulos, G., Avoli, M. and Gloor, P. (1982). *In* "Adv. in Epileptiology, XIIIth Epilepsy International Symposium" (H. Akimoto, H. Kazamatsuri, M. Seino and A. Ward, ed.), pp. 489–492. Raven Press, New York.

McGinnis, M. Y., Gordon, J. H. and Gorski, R. A. (1980). *J. Neurochem.* **34**, 785–792.

Macko, K. A., Jarvis, C. D., Kennedy, C., Miyaoka, Shinohara, M., Sokoloff, L. and Mishkin, M. (1982). *Science* **218**, 394–397.

McIlwain, J. T. (1976). *In* "International Review of Physiology, Neurophysiology II, **10**" (R. Porter, ed.). University Park Press, Baltimore.

Meldrum, B. (1979). *In* "GABA-Neurotransmitters" (P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod, ed.), pp. 399–405. Munksgaard, Copenhagen.

Meldrum, B. (1982). *In* "Psychopharmacology of Anticonvulsants" (M. Samdler, ed.), pp. 62–78. Oxford University Press, Oxford.

Meldrum, B. and Anlezark, G. (1981). *In* "Apomorphine and other Dopaminomimetics. Vol. 2. Clinical Parmacology" (G. U. Corsini and G. L. Gessa, ed.), pp. 25–31. Raven Press, New York.
Meldrum, B. S., Balzano, E., Gadea, M. and Naquet, R. (1970). *Electroenceph. clin. Neurophysiol.* **29**, 333–347.
Meldrum, B. S., Croucher, M. J., Badman, S. and Collins, J. F. (1983a). *Neuroscience Lett.* **39**, 101–104.
Meldrum, B. S., Croucher, M. J., Czuczwar, S. J., Collins, J. F., Curry, K., Joseph, M. and Stone, T. W. (1983b). *Neuroscience* **9**, 925–930.
Meldrum, B. S. and Horton, R. W. (1971). *Brain Res.* **35**, 419–436.
Meldrum, B. S., Horton, R. W. and Toseland, P. A. (1975). *Arch. Neurol. (Chicago)* **32**, 289–294.
Menini, Ch. (1976). *J. Physiol. (Paris)* **72**, 5–44.
Menini, Ch., Silva-Comte, G., Stutzmann, J. M. and Dimov, S. (1981). *Electroenceph. clin. Neurophysiol.* **52**, 42–49.
Menini, Ch., Stutzmann, J. M., Laurent, H. and Naquet R. (1980). *Electroenceph. clin. Neurophysiol.* **50**, 356–364.
Naquet, R. and Meldrum, B. S. (1972). *In* "Experimental Models of Epilepsy" (D. P. Purpura, J. K. Penry, D. B. Tower, D. M. Woodbury, R. D. Walter, ed.), pp. 373–406. Raven Press, New York.
Naquet, R. and Menini, Ch. (1972). "EEG Supplement No. 31, Recent Contributions to Neurophysiology" (J.-P. Cordeau and P. Gloor, ed.), pp. 13–26. Elsevier, Amsterdam.
Newmark, M. E. and Penry, J. K. (1979). "Photosensitivity and Epilepsy: A Review". Raven Press, New York.
Park, D. M., Darby, C. E. and Wilkins, A. J. Paper presented at the 14th Epilepsy International Symposium, London, 1982.
Pettigrew, J. D. and Daniels, J. D. (1973). *Science* **182**, 81–83.
Quesney, L. F. (1981). *In* "Neurotransmitters, Seizures and Epilepsy" (P. L. Morselli, K. G. Lloyd, W. Löscher, B. Meldrum and E. H. Reynolds, ed.), pp. 263–274. Raven Press, New York.
Quesney, L. F., Andermann, F., Lal, S. and Prelevic, S. (1980). *Neurology* **30**, 1169–1174.
Reader, T. A., Champlain, J. and Jasper, H. (1976). *Brain. Res.* **111**, 95–108.
Reader, T. A., Ferron, A. and Descarries, L. (1979). *Brain Res.* **160**, 217–229.
Ribak, C. E. (1978). *J. Neurocytol.* **7**, 461–478.
Ribak, C. E., Harris, A. B., Vaughn, J. F. and Roberts, E. (1979). *Science* **205**, 211–214.
Roberts, P. J., Foster, G. A., Sharif, N. A. and Collins, J. F. (1982). *Brain Res.* **238**, 475.
Rowan, A. J., Binnie, C. D., Warfield, C. A., Meinardi, H. and Meijer, J. W. A. (1979). *Epilepsia* **20**, 61–68.
Sillito, A. M. (1979). *J. Physiol. (London)* **289**, 33–53.
Silva-Comte, C., Velluti, J. and Menini, Ch. (1982). *Electroenceph. clin. Neurophysiol.* **53**, 479–490.
Sloper, J. J., Johnson, P. and Powell, T. P. S. (1980). *Brain Res.* **198**, 204–209.
Sloper, J. J. and Powell, T. P. S. (1979). *Phil. Trans. roy. Soc. B.* **285**, 199–226.

Small, J. G. (1971). *Clin. Electroenceph.* **2**, 78–88.
Soso, M. J., Lettich, E. and Belgum, J. H. (1980). *Epilepsia* **21**, 301–312.
Stutzmann, J. M., Laurent, M., Valin, A. and Menini, Ch. (1980). *Electroenceph. clin. Neurophysiol.* **50**, 365–374.
Traub, R. D. and Wong, R. K. S. (1982). *Science* **216**, 745–747.
Tootell, R. B., Silverman, M. S. and DeValois, R. L. (1981). *Science* **214**, 813–815.
Wallis, C. J. and Luttge, W. G. (1980). *Neurochemistry* **34**, 609–613.
Wastell, D. G., Wilkins, A. J. and Darby, C. E. (in press). *J. Neurol. Neurosurg. Psychiat.*
Watkins. J. C. and Evans, R. H. (1981). *Ann. Rev. Pharmacol. Toxicol.* **21**, 165–204.
Wilkins, A. J., Darby, C. E. and Binnie, C. D. (1979). *Brain* **102**, 1–25.
Wilkins, A. J., Binnie, C. D. and Darby, C. E. (1980). *Progress in Neurobiology* **15**, 85–117.
Wilkins, A. G., Binnie, C. D. and Darby, C. E. (1981). *Electroenceph. clin. Neurophysiol.* **52**, 461–468.
Wilkins, A. G., Zifkin, B., Andermann, F. and McGovern, E. (1982). *Ann. Neurol.* **11**, 608–612.
Wyler, A. R. and Ward, A. A. (1980). *In* "Epilepsy: A Window to Brain Mechanisms" (J. S. Lockard and A. A. Ward, ed.), pp. 51–68. Raven Press, New York.