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*REVIEW ARTICLE*

# Surgery for malformations of cortical development causing epilepsy

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## Summary

**Malformations of cortical development (MCD) are responsible for many cases of refractory epilepsy in adults and children. The results of surgical treatment are difficult to assess from the published literature. Judging from the limited number of adequately reported cases, approximately 40% of all cases of MCD treated surgically may be rendered seizure-free over a minimum 2-year follow-up period. This figure is the same for focal cortical dysplasia (FCD), the most common variety of MCD in surgical reports. In comparison with outcome for epilepsy associated with hippocampal sclerosis, this figure is low. Part of the difference may be artificial and related to limited reporting. Much of the difference is likely to relate to the complex underlying biology of MCD. Analysis of epileptogenesis in MCD has been undertaken. Different types of MCD have different sequelae. Some varieties are intrinsically epileptogenic; these include FCD and heterotopia. Although in most cases, the visualized MCD lies within the region of brain responsible for generating seizures (the epileptogenic zone), it may not constitute the entire epileptogenic zone in all cases. For polymicrogyria and schizencephaly in particular, the visualized abnormalities are probably not the most important component of the epileptogenic zone. There is evidence that the epileptogenic zone is spatially distributed and also, in some cases, temporally distributed. These findings may explain poor surgical outcome and the inadequacy of current presurgical evaluative methods. New preoperative techniques offer the opportunity of improved presurgical planning and selection of cases more likely to be rendered seizure-free by current surgical techniques. Of paramount importance is improved reporting. The establishment of a central registry may facilitate this aim. Specific recommendations are made for surgical strategies based on current experience and understanding.**

**Keywords**: epilepsy surgery; malformation of cortical development

**Abbreviations**: ECoG = electrocorticography; FCD = focal cortical dysplasia; HM = hemimegalencephaly; HS = hippocampal sclerosis; I/CED = ictal/continuous epileptogenic discharges; LIS = lissencephaly; MCD = malformation of cortical development; MD = microdysgenesis; MTLE = mesial temporal lobe epilepsy; PMG = polymicrogyria; PNH = periventricular nodular heterotopia; SZ = schizencephaly

## Introduction

Malformation of cortical development (MCD) describes a variety of structural abnormalities of the brain arising during gestation. In this review, the following entities will be considered: focal cortical dysplasia (FCD), characterized by dyslamination, abnormal cortical components and blurring of the grey–white interface; heterotopia, the presence of ectopic neurons in nodular or laminar aggregations, either in periventricular nodular or subcortical distribution; polymicrogyria (PMG) of unlayered and layered varieties, consisting of multiple small gyri, occasionally with fusion of the overlying molecular layers; schizencephaly (SZ), marked by a cleft with open or fused lips, passing through the entire thickness of the cortical mantle; lissencephaly (LIS), the absence of gyri, associated with gross cortical disorganization or the loss of specific neuronal laminae; and hemimegalencephaly (HM), in which varying combinations of the preceding pathologies are present enlarging an entire hemisphere. Detailed clinical, imaging and pathological aspects of these varied malformations are considered in a number of excellent monographs (e.g. Norman *et al*., 1995; Guerrini *et al*., 1996).

The application of MRI to epilepsy has revealed a higher

prevalence of MCD than previously recognized. In patients with refractory epilepsy, MCD may be seen in 8–12% of cases (Li *et al*., 1995; Semah *et al*., 1998) and in up to 14% of children with refractory epilepsy and retardation (Brodtkorb *et al*., 1992; Steffenburg *et al*., 1998). In a prospective incident study using high-resolution MRI in patients having their first seizure, 3% of cases with partial onset were found to have MCD (Everitt *et al*., 1998). Even with high-resolution MRI, MCD may remain undetected preoperatively and only be found at histology after surgery (Spreafico *et al*., 1998*a*; Ying *et al*., 1998), so that a proportion of the 25% of cases with refractory epilepsy and normal MRI (Li *et al*., 1995) may also harbour MCD. Therefore, current prevalence figures are probably underestimates. The management of epilepsy due to MCD thus presents a significant clinical issue. Most cases are refractory to medical treatment (Raymond *et al*., 1995*a*; Semah *et al*., 1998).

Surgical treatment of refractory partial epilepsy is gaining ground (Engel, 1996). For cases due to tumours or hippocampal sclerosis (HS), extensive surgical series confirm an excellent seizure outcome in a high proportion, typically 70–80%, of patients (Berkovic *et al*., 1995; Spencer, 1995; Engel, 1996; Eliashiv *et al*., 1997). This chance of becoming seizure-free is higher than that offered by modern antiepileptic drugs (Marson *et al*., 1996) and may generate benefits in quality of life beyond simply an improvement in seizure frequency (Vickrey *et al*., 1995; Sperling *et al*., 1996; Gilliam *et al*., 1997).

Surgical treatment is thus often considered for patients with refractory epilepsy due to MCD. The purpose of this review is to explore the surgical option in patients with MCD. The questions to be addressed are: does surgery have anything to offer? If so, then to which patients should it be offered? How should it be best directed? If it is less than perfect as a treatment, why is this? Can its efficacy be improved? The field is complex and incompletely understood, but some recent advances offer new insights into MCD biology and allow a more reasoned understanding of the role of surgery in the treatment of epilepsy associated with MCD.

## Surgery in epilepsy: literature issues

Epilepsy surgery is most commonly considered for the syndrome of mesial temporal lobe epilepsy (MTLE) due to HS (Engel, 1996). MTLE is a distinct syndrome with a known underlying substrate in the mesial temporal structures, even though debate about the precise pathology, mechanisms and aetiology continues (e.g. Shinnar *et al*., 1998). The homogeneity and definition of the key elements of MTLE facilitate its study. Comprehensive documentation has identified clinically useful prognostic indicators, guiding clinical decision-making and patient information (Engel, 1996).

In comparison with this gold standard, surgical data on MCD are much less complete. The dearth of information partly reflects incomplete understanding of MCD biology. Cases are individual in their seizure characteristics and their anatomy and pathology (Jay *et al*., 1993). Adequate surgical series of 'pure cultures' of MCD are not as large as those for MTLE and HS. Differing philosophies in different centres, for example, with respect to the meaning attached to epileptic discharges distant from the structural lesion, hinder the establishment of common ground. Meaningful prediction based on syndromic classification is difficult.

Non-biological issues complicate assessment of surgical outcome. The single most important variable is duration of follow-up. Although the most widely used outcome scale does not specify a minimum follow-up duration, quoted global outcome statistics employ a 2-year follow-up period (Engel *et al*., 1993). For refractory epilepsy due to HS, 96% of seizure recurrences after surgery occur within the first 2 years of follow-up (Sperling *et al*., 1996). Engel and colleagues have shown that irrespective of pathology, late recurrences may also develop (Engel *et al*., 1987). Paillas and colleagues documented recurrence in a still higher proportion of patients over a longer follow-up (Paillas *et al*., 1983). Bruton (Bruton, 1988), Gilliam and colleagues (Gilliam *et al*., 1997), and Döring and colleagues (Döring *et al*., 1999) report late recurrence for MCD specifically. The basis of recurrence may or may not differ for HS and MCD, but it does not seem unreasonable to set a minimum duration of follow-up when reporting outcome. While a period of 1 year might be considered adequate, the most rigorous current epilepsy surgery series favour a minimum of 2 years (Engel *et al*., 1993; Berkovic *et al*., 1995; Li *et al*., 1997). Unfortunately, for some large series of surgically treated MCD patients, no follow-up at all is given.

There are other significant issues concerning reporting. The absence of individual patient data is troublesome. Mean follow-up periods may be given without specific periods for individual patients. Follow-up scales may not be universally adopted or may be local modifications of Engel's scheme. Pathological diagnoses may not be clear or may be outmoded. Patients may be included inextricably in more than one series. For series with longer follow-up, certain data (e.g. MRI) may inevitably be unavailable. In many reports details are simply insufficient to allow meaningful interpretation. Reporting is improving, however, and there are sufficient data in the literature to allow discussion.

## Current outcome data for MCD surgery

The results of a survey of the English language literature detailing individual outcome from surgery for MCD with a minimum period of follow-up are given in Table 1. Studies provided only in abstract form have been excluded. Not all single case reports can be claimed to have been included, but it is hoped that most, if not all, series have been included. The outcome measure chosen is stringent: seizure-freedom (class I) according to the Engel scale. This criterion has been adopted to permit comparison with outcome figures for HS and because, at least following temporal resection in adults,

**Table 1** *Outcome of surgery for MCD: review of adequate literature published since 1971*

| Minimum duration of follow-up | Numbers | All MCD pathologies | | FCD only or main pathology FCD | |
|---|---|---|---|---|---|
| | | Series only | Series and single cases | Series only | Series and single cases |
| 1 year | All | 353 | 373 | 204 | 218 |
| | Seizure-free (%) | 152 (43%) | 168 (45%) | 77 (38%) | 88 (40%) |
| 2 years | All | 197 | 214 | 98 | 113 |
| | Seizure-free (%) | 80 (41%) | 92 (43%) | 35 (36%) | 44 (39%) |

Seizure-free is Engel class I or equivalent (Engel *et al*., 1993). Series defined as reports with at least two patients. Series and reports included: Taylor *et al*., 1971; Lindsay *et al*., 1987; Bruton, 1988; Hopkins *et al*., 1991; Leblanc *et al*., 1991; Palmini *et al*., 1991, 1995; al Rodhan *et al*., 1992; Landy *et al*., 1992; Salanova *et al*., 1992, 1995; Verity *et al*., 1992; Chugani *et al*., 1993; Desbiens *et al*., 1993; Fish *et al*., 1993*b*; Hirabayashi *et al*., 1993; Kuzniecky *et al*., 1993, 1995, 1997; Rintahaka *et al*., 1993; Khanna *et al*., 1994; Silbergeld and Miller, 1994; Taha *et al*., 1994; Bass *et al*., 1995; Carmant *et al*., 1995; Dubeau *et al*., 1995; Laskowitz *et al*., 1995; Montes *et al*., 1995; Pedespan *et al*., 1995; Raymond *et al*., 1995*a*; Saint Martin *et al*., 1995; Guerrini *et al*., 1996; Olivier *et al*., 1996; Pinard *et al*., 1996; Wyllie *et al*., 1996*a*, *b*, 1998; Barkovich *et al*., 1997; Kilpatrick *et al*., 1997; Li *et al*., 1997, 1999; Maehara *et al*., 1997; Shaver *et al*., 1997; Chan *et al*., 1998; Jambaque *et al*., 1998; Keene *et al*., 1998; Mukahira *et al*., 1998; O'Brien *et al*., 1998; Ryvlin *et al*., 1998; Sandok and Cascino, 1998; So, 1998; Spreafico *et al*., 1998*b*; Swartz *et al*., 1998; Szabo *et al*., 1999; Bastos *et al*., 1999; Bautista *et al*., 1999; Caraballo *et al*., 1999; Eriksson *et al*., 1999; Gleissner *et al*., 1999; Li *et al*., 1999; Mathern *et al*., 1999; Morioka *et al*., 1999; Sugimoto *et al*., 1999; Thom *et al*., 1999; Whitney *et al*., 1999; Hashizume *et al*., 2000. Cases with dual pathology are included.

decreased mortality and increased employment are associated with seizure-free outcome, but not with seizure reduction (Sperling *et al*., 1995, 1999). In children, a reduction in seizures may allow developmental progress (Duchowny *et al*., 1996). In the treatment of epilepsy, the ideal outcome must still be seizure-freedom (Walker and Sander, 1996). Quality of life measures have not been taken into account because so few series report outcome for this measure.

The most striking outcomes of this survey are (i) the small number of cases and (ii) the poor outcome in comparison with surgery for HS. Over 5000 cases of surgery for MTLE had been reported by 1990 alone (Engel *et al*., 1993); of these, about 70% of cases were free of seizures postoperatively for at least the last 2 years to follow-up. The paucity of MCD cases cannot be attributed only to the survey's stringent inclusion criteria. Older series could not benefit from MRI, so fewer cases may have been considered for surgery than might be the case now. The provision of adequate follow-up data in larger series might have altered the seizure-free percentage in this survey. Recent large series (e.g. Edwards *et al*., 1998) suggest that 50–60% seizure-free outcome may be the best obtained. As the proportion of studies using high-resolution MRI increases, it may be that the proportion of patients becoming seizure-free rises. There is a danger, however, that continuing incomplete reporting will perpetuate a potentially misleading view of outcome from surgery for MCD. Currently, compared with outcome for other apparently focal pathologies treated surgically for epilepsy, outcome is clearly less good.

Outcome is no better, purely in terms of seizure-freedom, for surgery performed in childhood (ages 1–16 years) as opposed to adulthood (over 16 years), within the limitations to analysis imposed by the reported data (Table 2). This does not take into account quality of life measures or the benefit that even temporary cessation of seizures may have during development. Outcome may seem excellent for surgery in infancy (Table 2), but refractory epilepsy occurring at this age is quite different from that occurring later. Comparison with later surgery figures would not be appropriate.

**Table 2** *Outcome by age at surgery: adequately documented cases only (series and single reports)*

| Minimum duration of follow-up | Numbers | Age (years) | | |
|---|---|---|---|---|
| | | <1 | 1–16 | >16 |
| 1 year | All | 25 | 122 | 120 |
| | Seizure-free (%) | 14 (56) | 56 (45) | 36 (30) |
| 2 year | All | 14 | 49 | 56 |
| | Seizure-free (%) | 8 (57) | 20 (40) | 20 (36) |

Results are given for all MCD pathologies; seizure-free is Engel class I only.

With respect to location of surgery (Table 3), again within the limitations of the data, there is probably little difference between temporal and extratemporal surgery in the literature overall. Recent detailed individual studies support this view (Edwards *et al*., 1998). Hemispherectomy can only rarely be performed in view of the neurological deficits inevitably incurred. The outcome is therefore not comparable with surgery for MCD as a whole.

In Tables 2 and 3, the numbers of cases included are considerably smaller than the numbers in Table 1; this reflects difficulties in extracting information. However, beyond the vagaries of series selection and publication bias, the relatively

**Table 3** *Outcome by location of surgery: adequately documented cases only (series and single reports)*

| Minimum duration of follow-up | Numbers | All MCD pathologies | | | FCD only or main pathology FCD | | |
|---|---|---|---|---|---|---|---|
| | | Temporal* | Extratemporal | Hemispherectomy† | Temporal* | Extratemporal | Hemispherectomy† |
| 1 year | All | 124 | 152 | 60 | 78 | 127 | 13 |
| | Seizure-free (%) | 40 (32) | 53 (35) | 35 (58) | 33 (42) | 43 (34) | 5 (38) |
| 2 years | All | 59 | 67 | 43 | 40 | 42 | 8 |
| | Seizure-free (%) | 19 (32) | 23 (34) | 25 (58) | 14 (35) | 16 (38) | 2 (25) |

Seizure-free is Engel class I only. *Some component of surgery involved temporal lobe (exact extent may be undefined); †included in this category are patients who had partial resections initially but went on to have hemispherectomy.

poor outcome must reflect either an inadequacy of current surgical programmes or a biological feature of the underlying MCD. These interlinked issues are considered next.

## Evaluation of the epileptogenic zone: current methods

Engel has stated, in relation to epilepsy surgery in general, '. . . the objective of presurgical evaluation is to identify the area of brain most responsible for generating habitual seizures and to demonstrate that it can be removed without causing additional unacceptable neurologic or cognitive deficits. There is no simple test to delineate the epileptogenic zone, defined as the volume of brain tissue necessary and sufficient for the generation of seizures' (Engel, 1996).

Historically, the epileptogenic zone was defined on functional grounds, using information from clinical findings (aura and ictal semiology; fixed, ictal or postictal neurological deficits) and EEG (most commonly scalp, possibly supplemented by acute or chronic intracranial studies). Additional functional methods may now be employed (PET, SPECT, functional MRI). However, numerous studies have shown that failure to resect an imaged underlying structural abnormality, or the absence of such an abnormality, is likely to lead to a poor outcome whatever is noted in other tests (e.g. Awad *et al*., 1991; Fish *et al*., 1991; Wyllie *et al*., 1994; Zentner *et al*., 1995; Ferrier *et al*., 1999). Thus, in current presurgical evaluations, much attention is paid to static neuroimaging findings (Engel *et al*., 1993; Wyllie *et al*., 1998; Scott *et al*., 1999), even though they cannot identify malfunction associated with an epileptogenic zone. Experience has led to an implicit construct identifying structural abnormalities, especially HS and MCD, with the epileptogenic zone.

The equation of the epileptogenic zone with underlying structural abnormalities parallels the general belief that completeness of resection of overt MCD, however identified, is the key to successful surgical outcome (Awad *et al*., 1991; Palmini *et al*., 1991, 1994, 1995; Wyllie *et al*., 1994, 1996*a*, 1998). However, few published data actually substantiate this claim. Most authors do not comment on how completeness of resection was actually judged. Others determine extent of resection by visual inspection at surgery. However, MCD, particularly FCD, may not cause any obvious alteration to normal cortical features (Palmini *et al*., 1995; Ying *et al*., 1998). EEG-based methods and neuroimaging offer the prospect of more rigorous determination of the completeness of resection of the epileptogenic zone or the malformation.

### *The role of EEG*

Scalp EEG findings in patients with MCD are diverse (Raymond and Fish, 1996), often showing widespread or multifocal interictal spiking, and tend to poorly localize ictal onset. Raymond and colleagues reported focal or lateralized interictal epileptiform discharges on scalp EEG in only 51 of 100 patients with localized MCD (Raymond *et al*., 1995*a*). Epileptiform discharges were often more widespread and sometimes only evident at sites distant from that anticipated by clinical features or imaging. Palmini and colleagues reported preoperative scalp EEGs in 30 patients with focal MCD (Palmini *et al*., 1991). Only one-third had EEG findings suggesting abnormalities confined to one lobe. Half the patients had multilobar interictal spiking, three patients had bitemporal and two generalized interictal abnormalities. Of 12 patients with apparently localized MCD reported by Hirabayashi and colleagues, only four showed localized interictal spiking (Hirabayashi *et al*., 1993). Kuzniecky and colleagues reported predominantly unilateral spiking in eight of 10 patients with temporal lobe MCD (Kuzniecky *et al*., 1991). However, in patients with frontal lobe MCD, only two of 11 showed focal spiking. These scalp EEG studies therefore demonstrate a high incidence of widespread interictal spiking in patients with focal MCD. There is, however, a subgroup of patients who demonstrate recurrent, reasonably well-localized, or at least lateralized, continuous or near-continuous runs of interictal spikes (Guerrini *et al*., 1992; Ambrosetto, 1993; Raymond *et al*., 1995*b*). These scalp EEG changes presumably reflect highly epileptogenic underlying cortex, but do not exclude more widespread abnormalities.

The disconcerting non-congruence of EEG abnormalities and structural changes may be due to the limitations of scalp EEG or the complex anatomical distribution of MCD, with modulation of epileptiform discharges before recording on the surface. Focal ictal or interictal scalp EEG changes have rarely been used as the sole guide to the identification of the epileptogenic zone in MCD. Most authors have concluded

that scalp EEG studies do not correlate significantly with outcome (Hirabayashi *et al*., 1991; Palmini *et al*., 1991; Li *et al*., 1997; Döring *et al*., 1999), particularly with regard to ictal scalp EEG in MCD in infants (Wyllie *et al*., 1996*a*). As some patients have become seizure-free despite extensive scalp EEG changes, such findings should not preclude further presurgical evaluation. Thus, some authors have stopped altogether attempting to relate outcome to scalp EEG results (Edwards *et al*., 1998).

The role of intracranial recordings remains uncertain. The demonstration that some MCD have intrinsic epileptogenicity (Mattia *et al*., 1995; Palmini *et al*., 1995; Kothare *et al*., 1998; see below) suggests that detailed neurophysiological investigations should be helpful. Although many authors suggest that chronic subdural findings do not correlate with outcome (e.g. Hirabayashi *et al*., 1991; Wyllie *et al*., 1996*a*, 1998), there are insufficient published data to determine the place of chronic subdural recordings in management. Electrocorticography (ECoG) is widely used to guide resections intraoperatively (Desbiens *et al*., 1993; Kuzniecky *et al*., 1993, 1997; Wyllie *et al*., 1996*a*, 1998; Shaver *et al*., 1997; Chan *et al*., 1998; Keene *et al*., 1998). Most centres employ ECoG in locations identified by preoperative clinical and MRI findings (Bastos *et al*., 1999), precluding evaluation of ECoG alone. Palmini and colleagues recorded 'ictal/continuous epileptogenic discharges (I/CEDs)' from the surface of MCD cortex, and in some cases from surrounding cortex that appeared normal on inspection but was subsequently proven histologically to harbour MCD (Palmini *et al*., 1995). Completeness of resection of the cortex evincing I/CEDs, as demonstrated by disappearance of the I/CEDs on postoperative ECoG, was correlated with a significantly better outcome. However, nine of 12 patients showing disappearance of such ECoG abnormalities did not have an 'excellent' (Engel class I) outcome, and the disappearance of interictal spiking on ECoG did not predict a seizure-free outcome. The value of I/CEDs in defining the epileptogenic zone thus remains unclear. In fascinating reports, ECoG studies in some patients with SZ actually guided resections away from the visualized MCD to electrically more active regions, with, in all cases, more than 80% reduction in seizure frequency for at least a year of follow-up (Leblanc *et al*., 1991; Landy *et al*., 1992).

Chronic intracranial recordings may show independent epileptiform activity in MCD and other regions, spreading activity from other epileptogenic tissue (e.g. coexistent HS) and changes emanating from normal-appearing regions (e.g. Francione *et al*., 1994; Dubeau *et al*., 1995; Munari *et al*., 1996; Kothare *et al*., 1998; Bautista et al., 1999). Bautista and colleagues raise the possibility that chronic interictal recordings might better predict outcome than other measures in extratemporal epilepsy, on the basis that even modern neuroimaging methods might not reveal all the pathology present, and that this might be better revealed using intracranial recording (Bautista *et al*., 1999). They acknowledge the weakness of such methods, however. Chronic intracranial recordings, ECoG and subdural EEG suffer from limited spatial sampling: they can only provide information from recorded regions, not from unsampled areas. Thus, in the report of Li and colleagues, intracranial electrode studies were in fact deceptive, leading to temporal resections, whereas presumed epileptogenic MCD heterotopia were rarely recorded from and were usually left unresected, leading to a failure to render any patients seizure-free in their series (Li *et al*., 1997). These findings suggest the presence, in some cases, of more than one epileptogenic focus. Thus, widespread ECoG abnormalities were associated in one report with a worse postoperative seizure outcome (Hirabayashi *et al*., 1991). The individual contribution of ECoG to evaluation is therefore difficult to assess. It is far from clear that ECoG alone can fully define the epileptogenic zone in MCD. The findings overall suggest that different pathologies may need to be considered separately. These issues will be discussed further below. The possible influence of anaesthesia on ECoG has not been discussed, but is a complex and potentially confounding issue.

## *The role of MRI*

MRI has revolutionized the detection of MCD and has obvious potential in identifying the true extent of MCD (Shorvon, 1997) and of its resection. However, it is difficult to judge the impact of modern MRI techniques on outcome, as few studies address this question specifically. Some studies state that completeness of resection was judged using postoperative imaging (Palmini *et al*., 1991; Montes *et al*., 1995). There are reports of complete excision according to MRI not being associated with a seizure-free outcome (e.g. Spreafico *et al*., 1998*b*), attributed variously to 'inaccuracy in method of quantitating lesion resection' (Palmini *et al*., 1991) or the presence of MRI-occult pathology (Palmini *et al*., 1995; Aykut-Bingol *et al*., 1998).

In a preliminary report of the most comprehensive series (from the Cleveland Clinic) (Edwards *et al*., 1998; E. Wyllie, personal communication), extent of completeness of resection was judged by comparison of pre- and postoperative MRI data. A seizure-free outcome was achieved in 58% with complete resection and in 27% of those with incomplete resection. This is the first large series using modern MRI methods to report on outcome with respect to completeness of resection in MCD. The benefit to patients of a favourable outcome including possibly rare, non-disabling seizures cannot be denied, and it is of great interest that some patients with multilobar involvement became seizure-free. However, long-term follow-up is essential. In particular, it would appear that there remain patients (42% in this report) with apparently complete resection as judged by MRI who failed to become seizure-free, and it is from this group that most stands to be learnt. Whereas the postoperative findings in this group will be of interest, it remains possible that even standard high-resolution MRI may fail to reveal the entire extent of MCD,

so that perceived complete resection is, in fact, not necessarily complete resection of all the pathology present.

### *PET and SPECT*

There is little doubt that PET can identify MCD (Duncan, 1997); this has been histologically verified in many instances (e.g. Chugani *et al*., 1993; Wyllie *et al*., 1996*a*). In paediatric practice, PET may have a clinical role, revealing abnormalities that are otherwise difficult to detect, and leading to successful surgical intervention in a number of cases (Chugani *et al*., 1993; Wyllie *et al*., 1996*a*). MRI was reported to be normal in many of these cases, though it is not clear to what extent this would still be the case if state-of-the-art high-resolution scanners were employed. It is possible that PET will continue to be useful in infants because of the pattern of myelination in the immature brain.

In adults, there has been very little work demonstrating the utility of PET in presurgical evaluation. Most patients studied by PET have not proceeded to surgery. In a recent large series (Ryvlin *et al*., 1998), both flumazenil and fluorodeoxyglucose (FDG) PET were normal in two patients with minute or subcortical MCD, and both showed multilobar involvement in a case with FCD who was seizure-free over a 2-year follow-up after a simple 'lesionectomy'. In two other unoperated patients with mesial occipital MCD, both flumazenil and FDG PET results were concordant with MRI and intracranial studies.

SPECT has been shown to aid in the localization of the seizure focus in presurgical evaluation for epilepsy surgery (e.g. Cross *et al*., 1997). Although patterns of cerebral blood flow have been well documented in MTLE (Newton *et al*., 1992), studies may not be so reliable in extratemporal epilepsy, particularly if the injection is not truly ictal (Newton *et al*., 1995). It may be more difficult to achieve ictal injections in extratemporal epilepsy because there may not be an aura of useful length and the seizures themselves may be shorter. It is imperative that such studies are performed with concomitant video-EEG monitoring, as any delay in injection may mean the results show seizure spread rather than seizure onset (O'Brien *et al*., 1998).

Few patients with MCD have been studied. Series to date concentrate more on localization of seizure onset than on underlying pathology. However, where data are available, seizures arising from MCD usually demonstrate an area of hyperperfusion concordant with the lesion following an ictal injection (Aihara *et al*., 1997; Kuzniecky *et al*., 1997). In a series of 55 SPECT scans from 51 children undergoing evaluation for epilepsy surgery at the Great Ormond Street Hospital for Children (H. Cross, personal communication), of 11 with MCD confirmed histologically (nine demonstrated on MRI, one focal atrophy and one normal MRI), all demonstrated EEG focus-concordant lobar or multilobar hyperperfusion on ictal/postictal SPECT compared with interictal SPECT. Interictal scans alone demonstrated hypoperfusion in a smaller number of cases, with a tendency for wider areas of abnormality to be seen compared with ictal scans. These findings suggest ictal SPECT may be a useful tool in the presurgical evaluation of children with MCD. It may be particularly useful if MRI is normal or inconclusive, ictal hyperperfusion and interictal hypoperfusion raising the possibility of MCD. In extratemporal epilepsy, SPECT may provide a guide to invasive monitoring. Data available from SPECT may be enhanced by the use of computerized subtraction and MRI-coregistration techniques (SISCOM; O'Brien *et al*., 1998). SPECT data must be examined in conjunction with data from other investigations, with an awareness of the spatial resolution of SPECT. SPECT is a complementary method, helping to define the epileptogenic zone rather than being of critical importance. In the series of O'Brien and colleagues, three patients with MCD are reported (O'Brien *et al*., 1998); in two, SISCOM results were concordant with MRI, but were discordant with correctly localizing scalp EEG and MRI in another. As with all new methods, it is not always clear what the results mean and whether they identify the epileptogenic zone or reflect epiphenomena.

### *Summary of current investigational methods*

No current technique defines the epileptogenic zone in MCD reliably enough to guarantee a successful surgical outcome, echoing Engel's general statement (Engel, 1996). Even with the best current guide, high-resolution structural imaging with intraoperative ECoG, it is evident that complete resection, though probably necessary for a good outcome, is not always sufficient for such an outcome. Consideration of some aspects of the biology of MCD may explain the inability of current methods to delineate the epileptogenic zone.

## The biology of MCD

A biological limitation to surgical resection has long been apparent. This is the overlap between MCD and normally functioning brain tissue. Total disruption of function normally ascribed to a given cortical region is often found (Brown *et al*., 1993; Calabrese *et al*., 1994). However, specific function normally ascribed to an affected region may persist in modified fashion. A patient with gross bilateral posterior MCD (Fig. 1) had normal visual fields and function, as far as could be determined. Raymond and colleagues recorded (distorted) somatosensory evoked potentials in five of 13 patients with MCD affecting the appropriate central regions (Raymond *et al*., 1997). Leblanc and colleagues demonstrated that electrocortical stimulation over a dysgenetic posterior temporal gyrus led to interference with speech (Leblanc *et al*., 1995). Duchowny and colleagues found overlapping language representation and MCD (Duchowny *et al*., 1996). The complexities of the mixture of normal and abnormal neurons within MCD (Preul *et al*., 1997), of neuronal connections, and of the timing of maldevelopment with respect to synaptogenesis and functional commitment, may

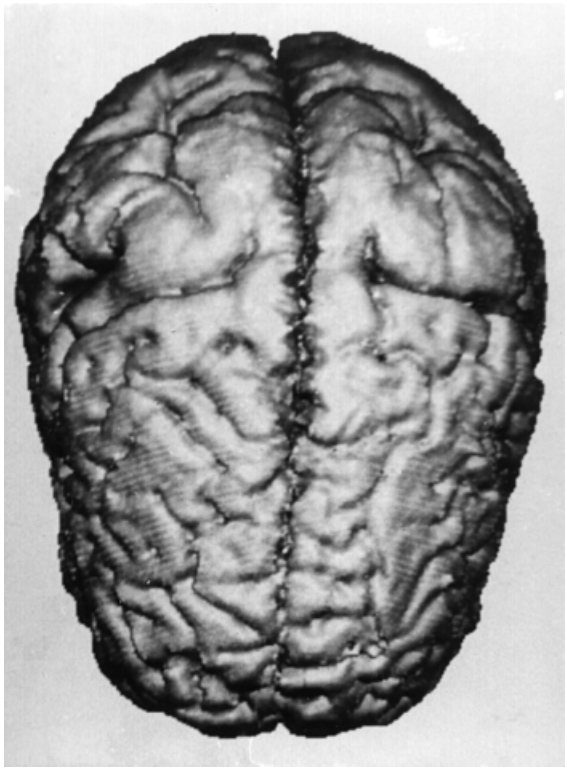

**Fig. 1** Vertical view (occipital pole at top of picture) of surface rendering of high-resolution MRI scan of patient with gross bilateral posterior macrogyria. The underlying diagnosis is probably pachygyria based on detailed analysis of the unreconstructed images.

explain why cortical function is not always reallocated to other regions. ECoG, with stimulation, is currently the best means of identifying eloquent cortex *in vivo*, and in cases where MCD abuts such cortex, ECoG may delimit the boundaries of resection. Clearly, this biological feature of some cases of MCD cannot be overcome by current surgical techniques. In addition, the structural substrate of the normal function (and indeed, the epileptogenesis) may be more locally dispersed than usual, confounding investigation dependent on changes in spatial density of information (e.g. functional MRI). When MCD is responsible for convulsive or focal motor status epilepticus, eloquent cortex may need to be sacrificed to stop seizures, even at the cost of a hemiplegia (Desbiens *et al*., 1993).

However, in many cases such biological limits do not apply, yet seizure-freedom is not obtained, even with complete resection of the epileptogenic zone. The question then arises: what evidence is there that MCD are intrinsically epileptogenic and contain the epileptogenic zone? While useful in assembling patients with developmental causes of refractory epilepsy, it must be remembered that a variety of conditions are included in the blanket term 'MCD'. Each type needs separate consideration.

## Varieties of MCD—correlation with clinical studies

There are many types of MCD. In some cases, the observed pathology does not fall neatly into one type and more than one category of MCD may coexist. For each category, the following aspects of biology may be addressed: animal models, intrinsic epileptogenicity, occult changes and dual pathology, and implications of genetic findings.

### *FCD*

In surgical series, FCD is undoubtedly the most common MCD. Current clinical opinion that as much of the lesion should be excised as possible is poorly supported for FCD. Most of the cases included in Table 1 do not comment on completeness of resection. There are cases which have become seizure-free despite histologically proven incomplete resection of visualized abnormality (Sisodiya *et al*., 2000), and cases not seizure-free despite completeness of resection according to the criteria used.

Experimental evidence favours intrinsic epileptogenicity in human FCD. Ferrer and colleagues (Ferrer *et al*., 1992), Spreafico and colleagues (Spreafico *et al*., 1998*a*) Ying and colleagues (Ying *et al*., 1998), and Mikuni and colleagues (Mikuni *et al*., 1999) have all demonstrated specific histopathological changes in human FCD compatible with increased excitability. Epileptiform EEG changes have been recorded from brain shown subsequently to contain FCD (e.g. Palmini *et al*., 1995), even when such FCD is not visible to the naked eye (Leblanc *et al*., 1995; Rosenow *et al*., 1998; Bautista *et al*., 1999), and resected human FCD maintained *in vitro* has been shown to generate the equivalent of epileptic activity (Mattia *et al*., 1995). In one case, intralesional EEG demonstrated epileptiform activity within FCD; in this interesting report, magnetic source imaging localized dipoles within the FCD in three of four cases (Morioka *et al*., 1999). In the other case, multiple dipoles were calculated, some of which lay outside the visualized abnormality. This patient did not become seizure-free after resection of the visualized abnormality, even with guidance by ECoG and depth electrode study.

Of all the MCD considered, the case for intrinsic epileptogenicity of MCD is best supported for FCD. Completeness of excision is thus likely to be important for seizure-freedom. However, not all FCD cases completely excised become seizure-free (Palmini *et al*., 1995). Overall, with no comment possible on the extent of resection, at best 38% of cases of FCD become seizure-free with surgery (see Table 1). Taylor and colleagues suggested that this may be because potentially epileptogenic FCD is distributed and may be non-contiguous: 'it may well be that other, if less ostentatious, areas of cortical dysplasia have been left behind. This possibility is supported by the fact that even within the limits of the resected lobes the abnormality was sometimes disseminated rather than confined to a single patch. The

degree, therefore, to which the brain as a whole may be affected remains uncertain' (Taylor *et al*., 1971). Whether this is the explanation for surgical failure in all cases is unclear, but merits exploration. Postoperative study of cases that have not become seizure-free is therefore vital.

Animal models of FCD are imprecise representations of the human condition. In one of the best models, excitability changes compatible with intrinsic epileptogenesis have been demonstrated (Redecker *et al*., 1998). However, these workers were also able to demonstrate in some cases identical excitability changes in surrounding histologically normal cortex, suggesting that 'cortical dysplastic lesions induce long-term functional alterations in structurally normal brain regions'. If such regions are normal on imaging and inspection and not studied by ECoG, or are suppressed by more active regions, then poor outcome might be explained, even when the visible abnormality and regions harbouring abnormal ECoG activity are excised. The biology of FCD may thus overcome current means of determining the epileptogenic zone.

## *Periventricular nodular heterotopia*

There is direct evidence for periventricular nodular heterotopia (PNH) intrinsic epileptogenicity in humans undergoing invasive electrical recordings (Dubeau *et al*., 1995; Li *et al*., 1997; Kothare *et al*., 1998; Spreafico *et al*., 1998*b*). This is underpinned by structural evidence of an imbalance between excitation and inhibition within nodules and of their connectivity to extranodular structures (Jensen and Killackey, 1984; Colacitti *et al*., 1998; Hannan *et al*., 1999). However, nodules are rarely localized (Raymond *et al*., 1994*a*), so that complete excision is rarely feasible. In addition, occult structural abnormalities in the overlying cortex have been described both histologically and on imaging and these may be of epileptogenic significance (Spreafico *et al*., 1998*a*; Hannan *et al*., 1999). Males in particular may have widespread cortical changes (Sisodiya *et al*., 1999). PNH is also the commonest MCD associated with the overt presence of more than one class of epileptogenic substrate, or 'dual pathology' (Raymond *et al*., 1994*b*; Cendes *et al*., 1995). The recent discovery of an X-linked gene thought responsible for familial bilateral PNH (Fox *et al*., 1998) compounds these issues, as other neurons may also be affected by the same mutation, especially in males. On these grounds, apart from females with visually isolated, completely resectable PNH, the theoretical chances of rendering a patient with PNH seizure-free surgically must be small. This is supported by the literature, notwithstanding that PNH have only recently been easily diagnosed on neuroimaging. In the largest series, epileptogenic activity was recorded from coexistent HS using intracranial electrodes, leading to temporal lobectomy in nine patients (Li *et al*., 1997). This was uniformly unsuccessful, the best result being obtained when the majority of the PNH was also excised. This provides perhaps the clearest example of dual pathologies, both being capable of epileptogenesis, explaining persistent seizures. Though probably widely applicable, this principle is rarely so dramatically demonstrated. The limitation of intracerebral recordings is highlighted by these findings; *de facto*, coverage is limited and results may be deceptive or incomplete.

## *Subcortical heterotopia*

Subcortical heterotopias (SH) are less common MCD. SH may occur in many forms, and may be so extensive or bilateral, as to preclude surgery altogether. SH may be associated with both PNH and abnormalities of overlying cortex (Barkovich *et al*., 1994; Guerrini *et al*., 1996). *A priori*, this suggests focal resection is likely to be ineffective. There are few adequately reported cases in the literature. Intralesional recordings have demonstrated epileptogenic activity arising within SH (Francione *et al*., 1994), although acute recordings have not always found this (Preul *et al*., 1997). Histology suggests an imbalance between excitation and inhibition (Hannan *et al*., 1999). Obviously incomplete excision of SH is associated with a poor outcome (Dubeau *et al*., 1995; Preul *et al*., 1997), whereas complete excision, as guided by intracerebral EEG, may lead to seizure-freedom (Francione *et al*., 1994). Recently, an animal model of bilateral laminar SH, which in humans may also be of genetic aetiology (Gleeson *et al*., 1999; Pilz *et al*., 1999), has been generated and termed *tish* (telencephalic internal structural heterotopia) (Lee *et al*., 1997). Neurons within the band heterotopia are known to be connected (Schottler *et al*., 1998), and *tish* mice have spontaneous seizures. Electrical recordings have not been reported. Given the poverty of human literature, further study of such models may give more insight into the epileptogenic characteristics of such malformed brains and, in particular, offer the chance of widespread examination of both structural and functional aspects, and the testing of hypotheses regarding seizure generation and propagation in SH.

## *PMG and SZ*

There are few published cases of surgical treatment of epilepsy in polymicrogyric MCD. Brodtkorb and colleagues report on excision of a region of PMG (completeness or otherwise of excision not stated) (Brodtkorb *et al*., 1998). Over the 10-month follow-up period, seizures continued unchanged, as did a unique and unchanged scalp EEG picture, leading the authors to speculate whether the histologically abnormal, resected MCD was indeed the source of the seizures. In a hemispherectomized child, non-contiguous, distant occult MCD has also been demonstrated (M. V. Squier, personal communication), further confirming the phenomenon of widespread pathology in many MCD.

In an animal model of PMG, it is the surrounding apparently normal-appearing cortex, rather than the malformed cortex, that is epileptogenic, as shown by transection experiments (Jacobs *et al*., 1999). Analysis of more distant areas of the

brain in these models was not reported. Thus, PMG seems to mark a brain that has suffered an insult and may help localize a visually occult epileptogenic region, but may not itself be epileptogenic. A poor outcome with resection of the MRI-visible abnormality should therefore not be entirely surprising.

SZ is among the rarest of MCD. It is characterized by a cleft extending through the thickness of the cortex, lined by PMG. Its aetiology may be genetic (Brunelli *et al*., 1996). There are currently no functional animal models of SZ, but by inference from PMG, SZ may not be intrinsically epileptogenic. Other areas of the brain may be histologically abnormal (Packard *et al*., 1997). It is intriguing that of the few cases reported in the literature, in most the cleft itself was not completely excised. In four cases, significantly improved seizure control was achieved by excision of adjacent epileptogenic tissue identified by ECoG or extraoperative intracranial studies (Leblanc *et al*., 1991; Landy *et al*., 1992); another case remained seizure-free for 5 years after extralesional temporal lobectomy (Silbergeld and Miller, 1994). In another case (Maehara *et al*., 1997), the lips of the cleft were excised under ECoG guidance and a seizure-free outcome achieved over the 1-year follow-up period.

Therefore, visible PMG and SZ may point to, rather than contain, the critical part of the epileptogenic zone. However, even with local exploration using ECoG, the entire extent of the MCD may not be revealed and other means are still required to identify this extent.

### *LIS*

There are few reports in the literature of focal surgery for LIS or pachygyria. LIS is usually too extensive an abnormality, associated with too severe a phenotype, to allow focal resection. No data are available from *in vivo* depth recordings from LIS and animal models have not been studied from this viewpoint (Majkowski, 1983). Given the recent discovery of genetic mutations underlying LIS (Reiner *et al*., 1993; Gleeson *et al*., 1999; Pilz *et al*., 1999), suggesting widespread neuronal involvement by the mutation, it would not be surprising if epileptogenicity, or at least widespread secondary connectional involvement, were widespread. Pathophysiological parallels with other MCD are therefore likely.

### *HM*

Debate continues about the nosology of HM. Histologically, the underlying MCD can usually be classified under one or more of the above categories. It is likely that the same strictures apply with respect to epileptogenesis. Abnormalities are more widespread. Hence, surgical treatment is usually by hemispherectomy. This is usually only contemplated in the presence of hemiparesis. Although the contralateral hemisphere usually appears normal, the presence of independent epileptiform changes over this hemisphere preoperatively is held by some to suggest the presence of additional pathology, manifest by a poorer outcome (Smith *et al*., 1991); others, however, do not find this (Carmant *et al*., 1995; Döring *et al*., 1999).

In at least one case of HM, MCD was found in an apparently normal contralateral hemisphere (Jahan *et al*., 1997). Most HM contain MCD for which this phenomenon has been reported. Further correlative studies are clearly required, as are means of detecting subtle MCD in the contralateral hemisphere.

### *Microdysgenesis*

That microdysgenesis (MD) is a pathological condition underlying some epilepsies has been popularized by Meencke (reviewed in Meencke and Veith, 1992). However, there is continuing uncertainty about its precise definition and significance (e.g. Lyon and Gastaut, 1985). Undoubtedly, abnormalities of cortical architecture that are more subtle than FCD do exist, manifest, for example, by an abnormal clustering of neurons, but difficulties in stereologically valid estimation of neuronal densities have hindered detection of MD. MD is usually reported in association with other pathologies, especially HS, making determination of its individual role difficult. This area is in need of clarification, particularly as MD may be the pathology underlying widespread or distributed additional pathology in other forms of MCD.

Thus, with the exception of PMG and SZ, most MCD are intrinsically epileptogenic, the MCD lying within the epileptogenic zone. For most MCD, however, pathology spreads beyond the visible MCD. In many cases, dysfunction may also be widespread: the epileptogenic zone is more extensive than the visualized MCD.

## Distributed epileptogenesis

Epileptogenesis is a complex and incompletely understood process. Despite decades of study, the basis of epileptogenesis, even in HS, remains unclear. Undoubtedly, the sclerosed hippocampus itself is involved in the disease process. Hippocampal resection is associated with cessation of seizures in some 70% of patients, but this does not imply that epileptogenesis and the epileptogenic zone are contained entirely within the diseased hippocampus. Indeed, the diversity of aurae, varieties of autonomic and psychomotor ictal manifestations, and possibly widespread neuropsychological deficits, all argue against a strictly localized disease process (e.g. Fish *et al*., 1993*a*; Dupont *et al*., 1998; Baxendale *et al*., 1999). Moreover, neuroimaging studies have shown a variety of subtle abnormalities in addition to atrophy of the hippocampus itself: additional extrahippocampal temporal, extratemporal, basal ganglia and ipsilateral hemispheric changes have all been reported (Sisodiya *et al*., 1997; DeCarli *et al*., 1998; Lee *et al*., 1998). The presence of these unsuspected additional changes may

be associated with a poorer outcome after surgery (Sisodiya *et al*., 1997). These additional changes may be secondary or associated with the underlying primary disease process. There is, of course, the possibility that at least some component of HS itself may be developmental rather than acquired in origin (Fernandez *et al*., 1998; VanLandingham *et al*., 1998), and that the visualized hippocampal atrophy is just the most visible part of a more widespread abnormality (Baulac *et al*., 1998).

Therefore, at least in some patients with HS, dysfunction that includes epileptogenesis may be distributed. Gloor hypothesized that persistent experiential aurae after temporal lobectomy might be due to 'distributed matrices' capable of maintaining the substance of an aura even after resection of part of a network responsible for its generation (Gloor, 1990). From stimulation studies in patients undergoing preoperative intracranial recordings, Fish and colleagues confirmed that the same aura could be generated by stimulation in disparate sites (Fish *et al*., 1993*a*). That seizures might also be generated similarly was not discussed but remains possible. A network of neurons distributed non-contiguously in the brain might be involved in the generation of seizures. However, despite circumstantial evidence, there is little direct proof. Surprisingly little is written about postoperative findings in patients who fail to become seizure-free after surgery.

It is tempting to link surgical failure blamed on a distributed epileptogenic zone with widespread structural abnormalities. Mesial temporal resection might be sufficient to inactivate a distributed epileptogenic zone in most cases, but in others the amount of the distributed network resected may not be sufficient to inactivate a more distributed epileptogenic zone. Time, too, may be a variable. Resection may remove enough of the epileptogenic zone to render a patient seizure-free for a certain period, but given sufficient time, the remainder of a distributed epileptogenic zone may be able to reorganize itself causing recrudescence (Berkovic *et al*., 1995). The epileptogenic zone ought to be thought of as having both spatial and temporal dimensions.

In some cases of HS there is obvious spatially distributed pathology: dual pathology. In general it is known, when lesions are present, that their removal is fundamental to a successful outcome (e.g. Fish *et al*., 1991). For dual pathology cases, removal of one may not be sufficient to render that patient seizure-free (Cascino *et al*., 1993; Li *et al*., 1997, 1999); removal of both abnormalities, where possible, is a better option (Li *et al*., 1999). Raymond and colleagues identified localized areas of MCD in 15% of patients using MRI or histological evidence of HS (Raymond *et al*., 1994*b*). In 25% of patients with MRI-identified MCD, significant hippocampal asymmetry has been found (Cendes *et al*., 1995). Ho and colleagues, studying patients with temporal lobe MCD, demonstrated a very high proportion (87%) of patients with either unilateral or bilateral dual pathologies (Ho *et al*., 1998). The possibility of dual pathology necessitates hippocampal measurements in all patients with MCD being evaluated for epilepsy surgery.

In terms of generating seizures, the distinction between overt 'dual pathology' and occult widespread pathology is purely semantic. Distributed occult MCD in addition to overt MCD might thus account for poor seizure outcome. This returns to the issue of what actually constitutes the epileptogenic zone in MCD. The most parsimonious operative definition is that the epileptogenic zone in MCD is that region of excision which leads to freedom from seizures over a defined period of follow-up. The latter addition to the definition is important: some patients who are initially seizure-free may develop seizures without a second precipitating factor after some years. The dynamic and distributed properties of epileptogenesis in MCD may be reflected in some results of tests currently used to identify the epileptogenic zone, manifest as non-concordant or widespread abnormalities at one time (e.g. Raymond *et al*., 1995*a*; Sisodiya *et al*., 1995; Richardson *et al*., 1996, 1998; O'Brien *et al*., 1998; Ryvlin *et al*., 1998; Morioka *et al*., 1999) or changing abnormalities over time (e.g. Raymond *et al*., 1995*b*; Palmini *et al*., 1997; Döring *et al*., 1999; Sisodiya *et al*., 2000). The epileptogenic zone in MCD may also be a changing spatiotemporal entity, possibly with different behaviour for different MCD.

This possibility is illustrated by a case of MCD treated surgically for refractory epilepsy. MRI had shown an abnormality in the right parietal cortex. Maximal interictal and ictal activity on scalp EEG recordings was noted at P4. Subdural grid recordings showed widespread frequent spike discharges; recordings during habitual seizures showed unifocal early electrographic changes preceding clinical change in all cases. Resection was performed under corticographic guidance. The superior and inferior parietal lobules, angular gyrus, superior cuneus, and superior and middle occipital gyri were removed. Histology of the resected $4 \times 1$ cm specimen showed FCD. Postoperatively, seizures of identical semiology recurred after 6 days and continued over the 5 years of follow-up. On EEG, 6 days after resection, a definite reduction in the spike discharge was noted over the previously active focus. Some time over the course of the following year, a new very active focus had developed, with phase-reversal over the mid-central area (T4 and C4), a clear shift noted despite the limited spatial resolution of scalp EEG. Some months later the focus had shifted inferiorly, and 2 years after surgery a single discrete focus could no longer be discerned. Seizure semiology did not change significantly over this period (R. Kennett, personal communication).

The rapid recurrence of seizures, despite excision of cortex with abnormal ECoG activity, suggests that a distributed epileptogenic zone already existed in this patient, perhaps manifest by the multifocal preoperative subdural interictal recordings. Seizure semiology did not change, suggesting that these distributed areas were acting in concert. The most active area, coterminous with the MRI abnormality, seemed

to have enslaved the network. Excision of the most active area released the rest of the network. Similar phenomena may underlie rapid cortical plasticity (e.g. Ziemann *et al*., 1998). The postulated networks may function in a hierarchical fashion, such that a dominant 'pacemaker' is able to entrain the rest of the network, as suggested by Awad and colleagues (Awad *et al*., 1991). The human cardiac conducting system is, of course, an excellent example of this behaviour. In summary, for many types of MCD, at any one time the complete epileptogenic zone may be more widespread than the visualized abnormality, even if the most active part of the epileptogenic zone (the 'pacemaker') is for most of the time contained within the visualized abnormality. The structural basis of such systems may be the widespread histological change reported in some MCD (see above).

If the epileptogenic zone in MCD is a distributed spatiotemporal entity, how can its components be identified? How also can the proportion of the epileptogenic zone that needs to be removed to stop seizures be determined? To date, the presence of persistent epileptogenic MCD tissue has been assumed in cases of surgical failure (e.g. Taylor *et al*., 1971; Awad *et al*., 1991; Palmini *et al*., 1991; Aykut-Bingol *et al*., 1998; Mukahira *et al*., 1998). Widespread histological examination of the brain is rarely feasible, as resections are of necessity minimized. Subtle MCD may be seen only at a synaptic level and thus not detected by routine histological study (Huttenlocher, 1974). Only in a few cases has there been histological proof of extensive abnormalities and this is usually by chance (Jahan *et al*., 1997). Intracranial EEG study, another possible tool for the detection of occult pathology (Bautista *et al*., 1999), also cannot be applied to large areas of the brain. In most cases, it is not possible to show histologically that other MCD is present or that other epileptiform dysfunction is present. Other means of examining the brain are required.

There are many ways of examining the whole extent of the cortex preoperatively. Some methods may allow detection of a potentially distributed epileptogenic zone. The widespread nature of scalp EEG changes in a high proportion of patients with MCD has been discussed. Although a few papers suggest that widespread changes are associated with a poor outcome, a thorough analysis, for example, on all the cases in Table 1, is not currently possible, but would seem worthwhile. New tools for the determination of potential coherence of multifocal interictal and ictal changes are becoming available, both for the temporal (Martinerie *et al*., 1998) and spatial aspects of distribution (e.g. objective quantitative neuroimaging methods). Detailed analysis of single cases may show that such phenomena do exist and stimulate more extensive study. The spatial resolution of scalp EEG may be enhanced by the use of multi-channel systems. Ideally, EEG or functional imaging would be performed after reversible presurgical inactivation of the postulated focus alone. This cannot currently be achieved, but intracarotid amylobarbital tests offer the chance of studying with EEG other parts of postulated networks, without the influence of the dominant lesion and other brain regions supplied by either the middle or posterior cerebral arteries. Neuroimaging methods alone may demonstrate widespread changes and rarely these have been shown to be of biological relevance (e.g. Chugani *et al*., 1993). The recent development of *in vivo* imaging of interictal epileptiform activity may provide further information (Krakow *et al*., 1999), especially if data are continuously acquired and analysed, bearing the possibility of distributed malfunction in mind. Magnetic source imaging may provide another means of examining distributed hierarchical networks (Morioka *et al*., 1999), especially if preconceived models of focal onset are not used to study real data. Although many of these methods are not widely available, a period of comprehensive evaluation in a cohort of patients might establish which test is most discriminatory in specific types of MCD. Sugimoto and colleagues report that in some cases, reoperation for MCD may improve outcome (Sugimoto *et al*., 1999); it may be that additional investigative methods can be used on cases that have failed to become seizure-free with a view to more complete excision of epileptogenic pathology.

The operational significance of additional abnormalities shown by these tests could only be determined by correlation with prolonged outcome measures. Perhaps only a proportion of patients with MCD can ever be helped by surgery, if, for example, the distribution of changes is too widespread for current surgical methods to tackle. In this case, the purpose of further study must be to identify the third of patients who will actually benefit from surgery. If newer surgical methods are developed, such studies might also help to direct their application. The importance of prolonged follow-up is clear. A central registry of cases might fulfil this need, facilitating assiduous reporting that need not depend on either follow-up at a tertiary referral facility or limited reporting opportunities.

## Conclusion

Overall, some 41% of patients with MCD, especially FCD, may be rendered seizure-free over a 2-year follow-up period by resective surgery (Table 1). This figure incorporates a broad sweep of studies, old and new; some newer studies suggest that this figure may be more of the order of 50% (e.g. Duchowny *et al*., 1998; Edwards *et al*., 1998; Keene *et al*., 1998; Eriksson *et al*., 1999). A proportion of patients may also be helped significantly, even if they are not rendered seizure-free, although seizure-freedom must remain the gold standard. Therefore, surgery should be considered seriously in patients with refractory epilepsy due to MCD detected on MRI.

Undoubtedly, however, careful presurgical evaluation is essential. Not all MCD are the same. Attempts should be made to make a presurgical diagnosis, because this may have implications both for further investigation and prognostication. In some cases, the visualized lesion may simply be a marker of more extensive abnormality. In other cases, genetic studies may reveal an underlying diathesis, allowing

both more careful classification and an indication of the likely extent of cerebral involvement. Developments in imaging technology may assist in diagnosis and in determination of the possible extent of underlying abnormality. All patients with MCD being considered for surgery should have preoperative EEG, MRI and PET studies (and if possible, SPECT, functional MRI and magnetoencephalography), with quantitative analysis. Extralesional regions should be studied in all cases. Intraoperatively, the exact role of ECoG in MCD surgery still needs to be defined. All cases should also be studied postoperatively, at least with EEG and MRI, so that excision may be quantified. Prolonged follow-up is of paramount importance.

Based on this review, the following guidelines might be posited. (i) For lesions that are thought to be FCD, limited subcortical and/or periventricular heterotopia without HS, excision of as much of the visualized lesion and as much ECoG-detected abnormality as possible should take place, within limits placed by encroaching eloquent cortex. (ii) For PMG and SZ, ECoG is especially important in guiding resection, as the visualized abnormality itself may not harbour the most active part of the epileptogenic zone. (iii) All patients with MCD being considered for surgery should have hippocampal mensuration. (iv) In the presence of overt dual pathology, such as HS, careful consideration needs to be given to the multiple contributions to the epileptogenic zone that are probably made by both pathologies; focal resection may include both pathologies. (v) The existence of additional, subtle, widespread components of the epileptogenic zone needs to be borne in mind; new methods for the detection of spatiotemporally distributed networks need to be developed and assessed.

These guidelines should be seen as hypotheses undergoing testing. Only the application of the entire armamentarium of presurgical investigations in all subjects being considered for surgery will enable us to offer the best care to such patients in the future. Engel has stated that such study should be considered part of the duty of care incumbent on epilepsy surgery centres (Engel, 1996). The setting up of a central registry for MCD may assist in this aim.

Surgery may be a crude instrument and we must hope that better understanding of MCD will lead to the development of better treatments, but in the meantime, it may be the best means currently at our disposal to improve the quality of life for people with refractory epilepsy due to MCD. Its further study is essential for this purpose.

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