

Alternative surgical procedures to help drug-resistant epilepsy – a review

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ABSTRACT – The concepts of pathophysiology of epilepsy which underly the non-resective surgical treatment of epilepsy are reviewed. The available techniques, lesioning, disconnection and stimulation are described and reviewed critically. Stereotactic lesioning, popular in the 1950's has been largely abandoned but stereotactic radiosurgery emerges as a useful technique, especially in the treatment of mesial temporal sclerosis. Disconnection by callosotomy has fewer applications than previously and multiple subpial transection (MST) has limited applications.

Stimulation is a technique with increasing usefulness. Vagus nerve stimulation (VNS) is an accepted method of treatment with low morbidity and mortality, which improves seizure control in at least 30% of patients, together with concomitant improvements in QOL and economic advantages. Stimulation of deep brain targets in the thalamus, subthalamus and mesial temporal structures is practical. There are indications that this improves seizure control in groups of patients previously unhelped by surgery, and this methodology has enormous potential.

KEY WORDS: epilepsy surgery, radiosurgery, vagus nerve, callosotomy, subpial transection, intracerebral stimulation

The origins of surgery for epilepsy are physiological rather than structural. The schools started in Montreal by Penfield and in Paris by Bancaud were physiological with identification of the focus by various functional means followed by an appropriate surgical resection. By the late 1960's there was clear evidence that focal epilepsy could be related to structural abnormality within the brain whose surgical removal could lead to complete and permanent alleviation of the seizures. The explosion of direct brain imaging, first CT in the late 70's and then MRI in the 90's led, quite rightly, to an explosion of lesion based surgery. These trends have overshadowed the valid

relationship between structural changes, physiological changes and clinically apparent seizures. This relationship has been studied both in the experimental and clinical situations, looking at phenomena such as kindling and secondary epileptogenesis. Unfortunately it is not possible to rationalise non-resective surgery on this basis with the confidence that resective surgery can be related to structural lesions. Many of the early procedures, such as callosotomy and cerebellar stimulation, were based upon anecdotal experimental evidence, which supported the intervention in general but did not stand up to rigorous or detailed examination. Patients consid-

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ered for non-resective procedures are often subject to multiple seizure types, many of which involve generalised or generalisation of seizures. The detailed pathophysiology of generalised or generalising seizures is little understood, and although some models will be discussed they have not proved to be effective bases for non-resective procedures. The hope expressed by Tailarach in 1974:

« L'idée qui a sans doute animé la plupart des opérateurs est celle de réaliser dans l'épilepsie une intervention prenant son modèle dans la chirurgie de la maladie de Parkinson »

Talairach et al., 1974

has not yet been realised.

Theoretical Considerations

There is a relapse rate, even for resective surgery, indicating that structural change alone is not the only arbiter of seizure control. Work on secondary epileptogenesis and kindling has shown that prolonged abnormal neurophysiological activity can lead to neurochemical changes in the brain. One has to presume that these changes are similar to the changes normally involved in laying down memory traces. The mechanism whereby such changes could be reduced is unclear.

Arousal mechanisms also play a part in these matters. In a significant number of patients with chronic epilepsy there is a relationship between alertness and seizure occurrence, attacks being much commoner in drowsiness or sleep. The old concept of centrencephalic epilepsy, which involved the thalamo-cortical relays driven from lower centres, may well be relevant to the genesis of generalised epilepsy. Many of the early models of epilepsy involved changes in the EEG, especially desynchronisation of the EEG, and these changes were used to justify some of the original procedures in non-resective surgery. The mechanism of this desynchronisation, and its relevance to the occurrence of clinical seizures, is not clear.

Recently, stimulation of the brain by various means has become more prominent. The way in which such stimulation influences clinical epilepsy is varied and three mechanisms may be considered. Stimulation may initiate arousal or a similar bilateral activation of the forebrain, or it may alter the properties of networks, after the manner of deep brain stimulation for movement disorder. Finally a unique focus may be identified which cannot be resected and which may be silenced by local stimulation.

Surgical Procedures

The available surgical interventions include lesioning, including stereotactic radiosurgery, disconnection and

stimulation. This review will not deal with other experimental procedures such as intracranial drug delivery, neural transplantation, gene therapy and so forth.

Lesioning

Stereotactic lesioning

It was popular and prolific in the 50's and 60's. The results were difficult to assess for a number of reasons. Presurgical assessment was less rigid, it was rare to be able to verify the site and size of the lesion and follow-up data were poor being short and inaccurate. At present there are no active centres in Europe and America pursuing this form of treatment.

Stereotactic radiosurgery

Has been an alternative means of creating lesions within the brain, which has recently been applied to drug-resistant epilepsy. This technique uses directed radiation to a target selected by brain stereotaxy. It has been used for many years for the treatment of arteriovenous malformations and tumours. The radiation is directed with a stereotactic frame and in young children requires general anaesthesia. This was pioneered by Barcia-Solario [1]. One clear disadvantage of stereotactic radiosurgery is the frequent lack of histological verification of the lesion, although those lesions for which it has been used recently commonly have a diagnostic MRI appearance. The mechanism of action is not entirely clear; there is not necessarily macroscopic destruction of tissue at the low levels of radiation used [2, 3]. The effect of the radiosurgery may take some months to appear and there may be some brain swelling as it acts. The long-term complications such as radiation necrosis and possible tumour induction are unknown but probably negligible. Regis and his colleagues have used radiosurgery to treat unilateral mesial temporal sclerosis and hypothalamic hamartoma [4]. In his most recent report there are 25 treated patients, all with unilateral mesial temporal sclerosis on MRI, selected using the usual criteria for microsurgical amygdalo-hippocampectomy [5]. In 18 patients follow-up of more than two years was available and 16 (81%) were seizure free, two more were improved. The mean interval to aura cessation was 10.5 months (range 6 – 21 months) and morphological changes were seen on MRI at 11 months (range 7 – 22 months). The only neurological consequence was an asymptomatic visual field defect in three patients. In their early studies Regis found that the dose was critical, and that the parahippocampal gyrus needed to be included within the target, and a report of failed treatment by Kawai *et al.* [6] used a dose that is less than that described by Regis and colleagues. In a multicentre study treating hypothalamic hamartoma Regis *et al.* describe ten patients, treated in seven different centres [7]. All had drug-resistant epilepsy with multiple seizure types

and a sessile hypothalamic hamartoma. Four patients became seizure free and there was a significant improvement in seizure control in four others. Although the lesions were not completely covered by the targeting, provided that the dose was around 17 grey, successful seizure control was attained. Side effects were rare; there was one patient with poikilothermia. There was an improvement in behaviour. These results are comparable with those obtained from conventional surgical approaches to these lesions.

Wang *et al.* described 31 patients, aged from one to twenty five years, with a mean age of 11.6 years, treated with the Gamma Knife. Some patients had MRI lesions but none were progressive and all were less than 2.0 cms in diameter. At follow-up, 12 patients had an Engel class I outcome (38.7%), two had an improvement (6.4%) and in nine there was no improvement (54.9%) [8].

Disconnection

Currently there are two credible procedures involving disconnection and these are division of the corpus callosum and multiple subpial transection.

Callosotomy

This is a long-standing procedure, which was based upon observations in experimental models of epilepsy and a fortuitous observation that seizures improved in a patient whose glioma had invaded the anterior corpus callosum. Van Wagenen and Herren first reported the procedure in 1940 [9]. The patients who were selected had generalised seizures and the operation, which aimed at total section, had a high morbidity and mortality. Wilson and his colleagues in Dartmouth, New Hampshire, after auditing their initial results, modified the surgery by using the operating microscope and staging the procedure so that the morbidity and mortality became more acceptable. It is recognised that callosal section rarely renders the patient seizure-free, data from the 1992 Palm Desert Symposium found only 5-7% of patients were completely free of seizures and a similar proportion was reported to the ILAE global survey [10, 11]. Drop attacks respond well to callosal section, generalised seizures and bouts of status less so. Partial seizures and myoclonic jerks may not respond and may even be made worse by the procedure [12]. The indications for the procedure are very unclear and emerge mainly from the known outcomes. Preoperative investigations are those used in most presurgical assessment programmes. A MRI may reveal technical obstacles to the surgery, including rarely the absence of the corpus callosum.

In patients without unilateral hemisphere disease bilaterally synchronous EEG discharges are considered to be the sole necessary indication for a callosotomy. The rationale for this procedure is far from clear. If patients undergoing callosal section had bilateral secondary synchrony where

one hemisphere drives the abnormal electrical discharges in both, then it might be supposed that callosotomy would be more likely to be effective in such cases. Matsuzaka *et al.* carefully analysed the degree of bilateral synchrony and morphological similarity of spike-wave discharges in 22 patients who underwent anterior callosotomy. Good outcome was seen with similarity of morphology of the spike-wave discharges [13]. In order to test this hypothesis we carried out carotid amytal tests on 18 patients prior to callosotomy. Where bilateral secondary synchrony appeared to be present there was often, but not invariably, a good outcome, but there was never a good outcome when it did not appear to be present. In patients of mixed cerebral dominance, difficulties can follow total callosal section. It is therefore prudent, wherever possible, to establish the pattern of speech distribution in individuals where it is in doubt, if for example they are left-handed or had significant but not overwhelming left hemisphere disease [14, 15]. The use of acute ECoG during callosal section to determine the extent of section has proved to be unreliable in predicting the outcome [16]. Any of the current neuro-navigator/image guidance systems using either the frame-based or frameless stereotaxy could be used to determine the extent of the section. It is valuable to assess the degree of section postoperatively using the MRI [17]. Callosal section is reported to be effective in improving the severe epilepsy, especially drop attacks, sometimes seen in bilateral band heterotopia and other bilateral forms of cortical migration neuronal disorder [18-20]. By contrast other methods such as localised resection or multiple subpial transection are ineffective [21]. It has also been used with good effect in catastrophic childhood epilepsy [22], in status epilepticus [23] and in patients with HHE syndrome [24]. Although the usual method of section is careful open microsurgery other methods such as stereotactic thermocoagulation and stereotactic radiosurgery have been proposed but are not in general use.

Complications from callosal section depend upon the extent of the section and the nature of the underlying disease process. The hemisphere should be approached from the known, or assumed, non-dominant side unless one hemisphere is damaged when the approach should be from that side. The complications are acute and chronic and related to the extent of the resection, being minimal with a truncal section and greatest with a total section. The acute complications are an appropriate hemiparesis, usually due to traction on the medial hemisphere surface, but occasionally due to venous insufficiency. There may be transient paresis, and akinetic mutism, probably the result of bilateral anterior cerebral artery spasm. In early series, reported before 1995, there is a significant incidence of both general and neurological complications although they tend to be transient. In our series of 33 patients undergoing anterior callosotomy, one patient died of post-operative pneumonia, two patients suffered transient bilateral anterior cerebral territory ischaemia, and a few pa-

tients had transient limb weakness and one an extradural haematoma. In recent series complications have been low and transient [25-28]. Quattrino and colleagues studied mutism in 36 patients subjected to callosotomy, it occurred in 10 patients; two had undergone a total section the remaining eight a partial section. The mutism always resolved varying in duration from 4-25 days, with a mean of seven days [29].

Two cognitive complications may follow callosal section. Speech may be affected in patients of mixed cerebral dominance, where interhemispheric communication is essential for the proper comprehension and production of speech and related functions. It has been suggested, but is by no means the universal opinion, that a carotid amygdalotomy test to establish speech dominance should precede the surgery in every case and operation, especially total section, refused to those of mixed dominance.

The second complication is the posterior disconnection syndrome, in which complex tasks requiring the utilisation of information from both hemispheres become impossible. First described by Sperry in 1977 [30] more details have emerged in subsequent studies. In some series the problem is dismissed, in others it is admitted but described as insignificant [31]. The overall occurrence is probably about 20%, is less so if the splenium is spared, and the practical significance is much less. Sass *et al.* note that when the language dominant hemisphere does not control the dominant hand there were always impairments [32].

Seizure outcome is difficult to assess. The usual scales for resective surgery are not appropriate. Oguni proposed that a 50% reduction in preoperative seizure frequency was an appropriate measure of good outcome [33]. The large numbers of results available over many years are consistent. The reduction in frequency of drop attacks is between 75-100% and of all epilepsies between 35-80%. The relief of partial seizures is much less certain. An analysis of our own material suggests that the seizure relief deteriorates over 2 years after surgery, although where the atonic attacks have been suppressed by the original operation they never return to their preoperative levels [34]. The question of whether completing the callosotomy is necessary to achieve the best result is open. A number of authors present evidence that seizure control can improve with completion of the section [26, 35, 36]. But it is also asserted that two-thirds anterior callosotomy is as effective as total section [37], and most groups would agree with Rossi that the first operation should be an anterior two-thirds section [28]. There are papers indicating improvements in quality of life [35, 36, 38, 39].

Callosotomy clearly is a possible treatment for patients with generalised seizures, and in particular for those with drop attacks and is probably also valuable for patients with frequent episodes of status epilepticus. In the first instance anterior two-thirds section is probably justified. Provided precautions are taken against operating on patients of

mixed hemispheric speech dominance then completion of the callosal section in patients who fail the anterior section is probably justified. However, it is legitimate to ask whether vagus nerve stimulation is a reasonable alternative. This will be discussed in detail later but it should be noted that the cost of callosal section is much less [25].

Multiple subpial transection (MST)

MST was conceived by the late Frank Morrell. The basis is that the epileptic discharges travel tangentially (horizontally) in cerebral cortex, whereas functional activity travels radially (vertically). Therefore, if the cortex is transected to the depth of the cortical ribbon, tangential transmission will be interrupted and vertical transmission preserved. To prevent discharge propagation from the isolated block the distance between the transections should be 5mm or less. Morrell and Whisler published their introductory paper in 1989 [40]. Patients with drug-resistant epilepsy originating from epileptogenic zones in primary motor sensory and speech cortex were selected for surgery after appropriate tests, including invasive recording where necessary. The appropriate area was exposed by craniotomy and acute ECoG was used to determine the end point of the transections. This end-point was when the epileptic discharges had been abolished or minimised. Technical difficulties arise when access to the cortex is difficult. Some confusion has arisen both from the original paper, and subsequent literature, between those patients in whom MST was performed together with a therapeutic resection and those in whom it was performed alone or with a biopsy. In general, the combination of resection and MST is more effective in controlling epilepsy than MST alone. This procedure is also useful in Landau-Kleffner syndrome, and has been used in children with multifocal epilepsy.

In the latest report from Chicago 84 patients were treated, some with resection, 49% of this group became seizure free and 37% of those treated with MST alone. Serious neurological deficit occurred in 7%, chiefly medial resections [41]. In a multicentre meta-analysis of 211 patients, 53 underwent MST without resection. In patients with MST plus resection, there was a greater than 95% reduction in seizure frequency in 87% of those with generalised seizures, 68% for complex partial seizures, and 68% for simple partial seizures. In MST without resection, the outcome was 71% for generalised, 62% for complex partial, and 63% for simple partial seizures. EEG localisation, age at epilepsy onset, duration of epilepsy, and location of MST were not significant predictors of outcome for any kinds of seizures after MST, with or without resection. New neurological deficits were incurred in 47 patients (22.3%) and were comparable in MST with resection (23%) or without (19%) [42]. Orbach *et al.* reports a relapse rate of 18.6% after several years [43]. MST has been used to control refractory status epilepticus [23, 44].

Paediatric reports include seven children with malignant rolandic-sylvian epilepsy who underwent resection and MST; three became seizure free and the remaining four had rare seizures [45]. Shimizu *et al.* used MST in 25 of 158 paediatric cases. There was no morbidity or mortality and ten patients had an Engel group 1 or 2 outcome and three had no benefit [46].

Target seizures were abolished in four of seven patients with Rasmussen's disease, but new seizure types appeared in these patients [47]. Schramm treated one patient with no benefit [48]. Nine patients with Rasmussen's syndrome were treated with MST in our service, five came to a second operation between two weeks and six months later. Two other patients were not suitable for further surgery and the diagnosis was a pathological diagnosis from a biopsy, their clinical course was not typical. The remaining two patients, one of whom had a frontal resection and MST, the other MST alone, both derived benefit taking them into Engel group 2A. Diffuse cortical dysplasia often involves eloquent cortex. Shimizu *et al.*, using transcranial magnetic stimulation, demonstrated hyper-excitability in an area of cortical dysgenesis in right central motor cortex. After transection the seizures were controlled and the hyper-excitability was abolished [49].

This procedure has been very effective in Landau-Kleffner Syndrome. Morrell believed that in some cases of Landau-Kleffner syndrome a single sylvian focus produced, through secondary epileptogenesis, a severe bilateral EEG disturbance. This EEG disturbance prevents the development of speech in the secondarily affected hemisphere. The mechanism is obscure but it is hypothesised that the hemisphere is unable to prune synapses preventing the development of appropriate pathways, a vital stage in brain development at this age.

In 1995, he described 14 patients treated with MST, obtaining improvements in language and behaviour in twelve [50]. The demonstration of ESES, a characteristic scalp EEG pattern with bilateral spike and wave occupying 85% or more of the sleeping EEG is necessary. The secondary epileptogenesis can be demonstrated by the pentothal suppression test in which the driving focus is inhibited last. The intracarotid sodium amytal (Wada) test can identify the driving hemisphere. It may be necessary to resort to intracranial recording if these tests fail. Because the focus is often in the Sylvian fissure, MEG may detect it when it is invisible to scalp EEG. Sobel *et al.* detected perisylvian spikes in 13 of 19 patients, although they were bilateral in ten [51]. In a group of four patients examined by Paetau a single intrasylvian focus was found in two patients showing a time course for the discharge corresponding to result of the methohexital suppression test [52]. A suitable MEG is now essential in the investigation of these patients. Improvement in language function, concomitant improvement in behaviour and improvement in the EEG are the criteria for a good outcome in these

patients. A study of untreated patients supports the argument that MST should be considered in a child who has had ESES for more than two years and who is not responsive to steroids particularly when behaviour is severely disturbed and fits are frequent [53]. Eighteen patients have been treated in Chicago, four of these patients failed to improve and one of our ten patients came into the same category, in retrospect they were all bad selections [54]. The experience at Rush and ours is similar with patients requiring both left and right-sided operations. In both series there was a rapid improvement in behaviour, a significant improvement in language function and good control of fits [54, 55]. There is a more controversial application of MST in patients with multiple epileptogenic areas and the syndrome of autistic regression. Patil and his colleagues believe that there is a connection between these patients and those with Landau-Kleffner syndrome [56]. The results of this surgery remain unreplicated and controversial.

Stimulation

Our concepts of the complex mechanisms, which determine seizure generation and propagation within the brain, are rudimentary and based upon animal experimentation and clinical observations that concentrate on selected areas and ideas. The idea of 'gating', whereby the excitability at a particular locus within the brain determines the threshold for seizures and therefore the chance of seizure propagation is unifying and useful. It reconciles the properties of networks and neurochemical pathways. The following simplified summary is drawn from a more detailed account by Proctor and Gale [57]. It is also worth noting Fisher's comment that animal models of epilepsy, and the experiments conducted with them are not always as uniform and consistent as one would wish [58].

Vagus nerve stimulation (VNS) affects the projections from the nucleus tractus solitarius, which are widespread to the forebrain structures, including the amygdala and hippocampus. There is also a serotonin-mediated pathway with widespread connections. Animal experiments show that the locus coeruleus, a small aggregation of cells on the floor of the fourth ventricle, has to be intact for VNS to exert its influence [59]. Widespread connections from this structure activate a noradrenaline pathway. In an animal model, Zagon and Kemeny showed that VNS induces a slow hyperpolarisation of cells in cortical layer V [60].

Findings from clinical studies in humans are less clear. Henry showed increased regional cerebral blood flow in the thalami, correlated with seizure control [61]. Conversely, SPECT studies showed deactivation of the left thalamus, not correlated with seizure control [62]. But they also reported that the response varied depending upon whether patients were studied acutely or after chronic stimulation. Chronic perfusion changes in the

right hippocampus correlated with long-term clinical efficacy of VNS and were consistent with brain deactivation [63]. A study with fMRI has shown widespread changes [64]. Most studies have failed to demonstrate any effect on the EEG from VNS but Koo *et al.* reported progressive changes with stimulation, first clustering of epileptiform discharges and then increasing spike-free intervals [65]. In one patient it was possible to show that epileptiform sharp waves recorded from a left hippocampal depth electrode were increased by VNS at 5 Hz and decreased by VNS at 30 Hz [66].

Lesions of the cerebellum will facilitate seizures in experimental models and stimulation of the cerebellum will reduce seizure induction in the forebrain in experimental models.

Experimental work involving the centro-median nucleus (CM) of the thalamus has shown that there is a relationship between arousal and seizure threshold such that when arousal is depressed, seizure threshold is reduced. The anterior nucleus (AN) of the thalamus, in appropriate models is activated during PTZ induced seizures. Most of the animal work relates to spike-wave discharges in cat and rat models. Early work indicated that stimulation of the CM in cats at 8-12 Hz would result in a widespread surface negative recruiting wave [67] whereas stimulation at > 60 Hz would desynchronise the EEG [68]. In the genetic model of generalised absence epilepsy the events between thalamic cells and neocortical cells have been well described both at an intracellular and extracellular level. In the GAERS rat model there seems to be a multi-path circuit involving the main thalamic nuclei, the cortex especially layer V and the nucleus reticularis thalamus-(nRt). This loop results in the nRt resetting the thalamic neurones so as to produce synchronisation, initiating rhythmic activity in the thalamus which affects the cortical neurones, in such a cycle it is not easy to identify initiation. Changes in the thalamic circuitry in the rat appear to be initiated from the nRt [69]. There are independent accounts in both rat and cat models describing the initiation of seizures in the cortex [70-72]. In a rat model low frequency stimulation of the anterior nucleus (AN) is proconvulsant whereas high frequency stimulation will raise the clonic seizure threshold [73]. Data from pharmacological experiments suggests that AN acts as a gating mechanism between the subcortical structures and the cortex and that there are clear electrophysiological links between AN and cortical activity in seizures [74, 75].

The general conclusion, derived from different approaches, is that there is a reciprocal relationship between the elements of a thalamo-cortical circuit and that this relationship can produce spike-wave discharges similar to those seen in human generalised absence epilepsy. The initiation of seizure activity in this circuit is from the cortex and the thalamus synchronises cortical activity. Therefore neurophysiological manipulation of thalamic activity may

be quite limited and influences from outside the thalamus, from subthalamic structures or the reticular formation may determine the frequency or occurrence of synchronised activity. One has to agree with Fisher's conclusion in 1992 that 'CM and related structures are involved in epilepsy but the role of CM and the efficacy of stimulation of CM in clinical epilepsy is not clear' [76].

Compared with these diffuse and general effects, it is thought that within the basal ganglia there is a network, which carefully balances excitation and inhibition. The exploitation of the discrete imbalance in this network has allowed the successful treatment of Parkinson's disease by deep brain stimulation. The basal ganglia contain a cascade of connections ending in the neurones around the superior colliculus. At each point in this cascade there is inhibitory activation, mediated by GABA, to counter an external excitatory input. Conversely, there are neurones in the superior colliculus, at the end of this chain, whose excitatory output increases resistance to seizures. Therefore if the inhibitory effect in the nigral-collicular section is reduced there will be increased anti-seizure effect. High frequency stimulation of the subthalamic nucleus would be expected to have this effect [77].

Finally, little is understood of the timecourse of changes induced by brain stimulation. Although the effect of deep brain stimulation in dopa responsive Parkinson's Disease is virtually instantaneous in other forms of movement disorder, such as dystonia the effect may take many months to appear, or become optimal even with little or no change in the stimulation parameters [78]. It is therefore clear that standardisation of stimulation regimes, agreement if possible on the time to optimal effect, and rigorous application of conditions for functional imaging will be important in clarifying the indications for these procedures and also elucidation the pathophysiology which they affect. Failure to take account of these factors, especially in high volume procedures such as vns, has led to inconsistency in investigating the effect of the stimulation and assessing the outcome.

Vagus nerve stimulation

VNS was introduced in the early 1990's, to date 11 000 of these devices have been implanted in adults and 5,000 in children. The data used to obtain FDA approval in the USA are in trial EO5 [79]. Selection for VNS, especially in children, is difficult. It is essential to show that the patient has epilepsy and video-telemetry may be necessary. More effective solutions, such as various resective procedures should be excluded and the patient and their relatives, or carers, should realise that vns is a less satisfactory solution. Therefore VNS should not be recommended outside of a multidisciplinary epilepsy surgery programme.

The left vagus nerve consists mainly of afferent fibres in humans and therefore was thought less likely to give

cardio-respiratory or other vagal effects. In desperate circumstances it can be implanted around the right vagus nerve, as we have in one adult. The generator delivers an intermittent stimulus to the nerve, in the usual configuration it is 'on' for 30 s and 'off' for five minutes although other possibilities are available. The usual frequency of the pulses within the train is 30 Hz and the pulsewidth 250 ms., although these parameters can be varied. The battery life depends upon the current drain and the latest devices are expected to have a battery life of 6-8 years. Brief application of a magnet will give an extra stimulus train, which is useful in some patients with warnings of their seizures. If the magnet is applied constantly it will turn the device off; stimulation is resumed immediately the magnet is removed.

There are side effects, those which occur whilst stimulation is 'on', and those which are not clearly related to the stimulus. The minor complications, due to stimulation of the nerve and local current spread are well known, comprising cough, hoarseness and local paraesthesiae. They are universally mentioned in all reports, adult and children alike, are recognised to be stimulus dependent and diminish with time [80]. There has been anxiety about effects on swallowing in mentally retarded children [81].

The cardiorespiratory effects of vagus nerve stimulation are few. Occasionally bradycardia or asystole occurs while testing the device during implantation [82]. Therefore we advise patients to turn the device off, using the magnet as described above, for the duration of a general anaesthetic. This phenomenon has not been reported in the waking state.

No clear effect on respiration has been reported. Lotvall *et al.* showed that FEV1 (forced expiratory volume in 1 s) was unaffected except in one patient with chronic obstructive airways disease who had a stimulation-dependent decrease in FEV1 [83]. A study by Annegers of 25 deaths in 1 819 patients treated with VNS, concluded that the mortality and SUDEP rates were similar to those seen in trials of new anticonvulsants and that there was no evidence of excess mortality. Interestingly, after two years, the SUDEP rate declined to less than would be expected [84].

There is now an enormous literature on the outcome of VNS. Only 3% of patients become seizure free with VNS, but many patients experience a reduction in the severity or frequency of their seizures. A summary of 440 patients treated found that the continuation rate was 96.7% at one year, 84.7% at two years and 71.2% at three years. The median percentage seizure relief was 35% at one year, 43.3% at two years and 44.1% at three years [85]. Privitera's Cochrane Review of mixed or adult series up to October 2000 concluded that VNS was a well tolerated and effective treatment with few side effects and none of the adverse side effects often seen with new anticonvulsant drugs [86]. Psychiatric disorders on suppression of seizures have been reported by one group where, among

81 patients with a seizure reduction of 75% or more, seven (9%) developed major disorders. Six became dysphoric, four with catastrophic rage, all seven had had psychiatric problems prior to treatment, they were managed with a combination of appropriate medication and in two cases reduction of stimulation [87]. This device should be viewed in the same way as an add-on drug, needing time to be adjusted for optimum effect. The effect improves with time over the first one to two years. It is difficult to identify 'responders'. Boon and colleagues suggested that patients who responded to the magnet were more likely to be long-term responders [88]. Kuba *et al.* studied interictal epileptiform discharges and found that when they were reduced, especially when the pulse generator was active, then a good outcome was seen [89]. Partial complex seizures probably respond best and there is mixed evidence that various seizure types or syndromes, or the presence of a structural abnormality, or previous surgery, affect the outcome.

Better results are reported in children than adults. Reports of the median seizure reduction at a stated time all show a consistent trend, improving with time, varying between 31% reduction at six months to 42% at 18 months [90, 91]. Patwardhan *et al.* analysed the effect on various seizure types in 38 children, seizure reduction was 80% for atonic seizures, 65% for absence seizures, 48% for complex partial seizures and 45% for generalised tonic-clonic seizures [92]. Very good results have been reported in Lennox-Gastaut syndrome with a median reduction of 58% at six months [93]. In the developmentally disabled Andriola and colleagues report a 50% reduction in 68% of these patients at six months [94]. Gates and colleagues note that patients living in residential accommodation, who are more severely affected by their disease, still benefit from VNS [95]. Although VNS has been shown to be effective in patients with bitemporal epilepsy [96] in patients who had undergone previous surgery Helmers *et al.* seemed to demonstrate that in patients who had undergone previous callosotomy the results were better. Both Helmers and ourselves showed that the response after other operations, particularly temporal lobectomy, was not particularly good [91, 97].

Improvement in quality of life (QOL) has been reported consistently, although different groups use different scales. Typical of the findings are those described in 17 patients by Ergene *et al.* They used the QOLIE-10 and tested patients before and at intervals up to one year after treatment and found a significant improvement in scores, independent of the effect on seizures [98]. In children, Frost *et al.* noted that QOL improved in some patients and Helmers *et al.* found improvements in alertness, verbal communication and school performance [91, 93]. Patwardhan *et al.* using a visual analogue scale completed by the patient's carer, found improvement in QOL in 86% [92]. There are clear economic benefits. Boon studied 16 adults and found a reduction in epilepsy related direct medical costs

(ERDMC) from 8 830 US \$ to 4 215 US \$. Majoie found a reduction in costs in children of 2 876 Euros in six months with a payback period, to recoup the initial cost, in 2.3 years [99, 100]. In straightened economic circumstances the Colombian experience suggests that other procedures, such as callosotomy, may be justified [101].

There is a controversy at present as to whether patients who would have been considered for callosotomy should now be offered VNS as the first surgical manoeuvre. On the whole the evidence suggests that, economic considerations apart, this would be recommended management.

Intracerebral stimulation for epilepsy

It was first proposed seriously by Cooper who published observations both from implanted electrodes on the cerebellum and in the anterior nucleus of the thalamus [102, 103]. Because blinded studies showed that cerebellar stimulation had no effect this treatment has been abandoned but Fisher believes that its potential has not been fully exploited [104-106].

About the same time Sramka, from observations using deep electrodes in the head of the caudate nucleus, began to use this as a lesioning target and subsequently as a stimulation site, and later similar work was undertaken by Chkhenkeli [107, 108]. The most experience in the West, using the centromedian nucleus of the thalamus is that gained by Velasco and his colleagues, their first publication was in 1987 [109]. Latterly further stimulation has been undertaken both of the centromedian nucleus and of the anterior nucleus of the thalamus.

As noted above, involvement of the nigral system in epilepsy had been studied extensively by Gale and also by Benabid [110, 111]. As a consequence both Benabid and Lûders have pursued this option.

Stimulation of these deep nuclei has been used in an empirical fashion for several different groups of patients. Sramka and Chkhenkeli have described the use of low frequency stimulation of the caudate nucleus, but their patient population is not clear [112, 113]. However, Velasco and Velasco have carried out the major work in this area. They have applied the technique to patients with generalised seizures as well as patients with partial and motor seizures. Subsequently, they have reported patients with Lennox-Gastaut syndrome. In 1993 they summarise their experience with 23 patients whose main seizure types were generalised tonic-clonic seizures (9), partial motor seizures (3), complex partial seizures (5) and tonic-clonic seizures associated with the Lennox-Gastaut syndrome (6). Fisher and colleagues then carried out a pilot controlled trial of thalamic stimulation for which they selected seven patients, six of whom had generalised seizures [114].

Both the Russian experience and that of the Velasco brothers involved attempts to identify areas, which might respond to stimulation by using chronic depth recording. It

was an important feature of the patients treated in Mexico City that the stimulation locus was partly determined by the ability to obtain a recruiting response at low frequency (6 Hz) and desynchronisation of the EEG at a higher frequency (60 Hz) [114]. More recently Velasco and colleagues have explored more thoroughly the effect of electrode placement on outcome [115]. Stimulation alternated between left and right electrodes in a one minute train with a four minutes interval between them. These stimuli were applied for two hours each day for three months. In the Fisher series the stimulation frequency was higher at 65 Hz and the individual square waves were briefer lasting only 0.1 mss compared with 1 mss in the Velasco series. The stereotactic techniques employed by the two groups were different, in the Velasco series stereotactic location was by using pneumoencephalography whereas in the Fisher series CT and MRI were used. There are number of other reasons for believing that the site and nature of the stimulus was different between the two series as explained by Velasco in 1993 [114].

Complications have been infrequent and minor. In the Velasco series there was one patient who sustain a scalp haematoma and another in whom there was transient swelling of the internal capsule due to mislocation of an electrode. There were three other instances of mislocation of electrodes and seven instances of external failure of leads and generators. In the Fisher group of patients there was one patient who had a generator failure and another to have an asymptomatic haematoma adjacent to one of the depth electrodes [76].

In respect of the caudate nucleus stimulation, the results of Chkhenkeli and his colleagues are relatively inaccessible but they describe good results from low frequency stimulation of the caudate nucleus alone or in combination with other structures.

The outcome in the Velasco series is much clearer. Looking at their four different groups of patients those with partial motor seizures (group B, Rasmussen's type) and there is generalized tonic-clonic seizures (group D, LGS type) showed improvement [114]. A subsequent analysis also suggested that generalized tonic-clonic seizures independent of Lennox-Gastaut syndrome also responded well and were accompanied by a decrease in interictal paroxysmal discharges [116]. They were also able to demonstrate significant improvements in cognitive function and background EEG waveforms in three of their four groups [117]. A more recent report has confirmed these findings [118]. In contrast, the Fisher study showed no benefit to seizure control but also suggested that the treatment caused no gross deterioration.

There is one recent report of anterior thalamic nucleus stimulation. Hodale *et al.* treated five patients in this way and obtained a decrease in seizure frequency of 54% [119]. Benabid has used the subthalamic nucleus as a target and in two reports describes reduction in seizure

frequency with high frequency stimulation in five patients [111, 120]. Finally, both Velasco and a Belgian group have described seizure controlled with electrodes implanted in the mesial temporal structures. In the Velasco studies the stimulation was applied subacutely in the course of pre-surgical evaluation with intracranial electrodes and both demonstrated an effect and no clear damage to the subsequently resected hippocampus [121, 122]. In the Belgian experience three patients received unilateral amygdalo-hippocampal stimulation for five months. There was a 50% reduction in seizures and in two patients anticonvulsant medication could be reduced [123].

Closed loop stimulation

It is different from the systems already described, which apply the stimulus irrespective of the patient's state. This methodology aims to detect the prodromal neurophysiological changes, which occur in advance of seizures and use these to deliver a stimulus. At present there is a very complex system which has been used subacutely in hospital described by Osorio *et al.* [124]. The Yale group has described a battery operated system which might be more practical [125]. Preliminary results from Osorio's laboratory suggest that some degree of control has been obtained with this method of stimulation [126].

Conclusion

1. These non-resective surgical options rarely produce complete freedom from seizures but have been shown to significantly improve seizure control significantly and to be accompanied by improvements in behaviour, cognition and quality of life (QOL).
2. Earlier surgical operations in this group probably now have a limited place.
3. Stimulation, apart from economic considerations, has considerable potential benefit, not least of which is extending treatment to groups previously excluded.
4. Vagus nerve stimulation is now an accepted method of treatment which:
 - a) should be applied after proper assessment;
 - b) shows benefits in seizure control, behaviour and QOL;
 - c) requires more rigour in its application.
5. Deep brain stimulation, although in its early stages, holds considerable potential. □

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