Frozen section in pituitary surgery

Most surgeons consider intraoperative frozen section examination as an important part of pituitary surgery.^{1,2} Frozen section is used to establish a histological diagnosis (adenoma, other tumours, hyperplasia, and non-neoplastic processes) and to examine the margins of resection and determine its adequacy.^{1,2} A reliable intraoperative histological diagnosis will help the surgeon with achieving the ultimate goal in pituitary surgery—namely, selective removal of the lesion with preservation of endocrine function.³ With the increased popularity of the transsphenoidal approach for microsurgical removal of pituitary lesions, mainly microadenomas, the reliability of the frozen section technique becomes even more important. It has been stated that the transsphenoidal route provides the surgeon with suboptimal exposure of the gland and therefore smaller pieces of tissue are submitted for evaluation by frozen section.^{4,5} Some authors suspect that this may result in a lesser degree of accuracy of the intraoperative rapid diagnostic techniques.^{4,5}

There are only a few papers in the English literature studying the accuracy rate of frozen section diagnosis of pituitary lesions.^{1-3,6} None of these compared the accuracy rate in trans-sphenoidal surgery with that of the subfrontal craniotomy approach.

We studied 55 cases of pituitary surgery. Twenty four operations were done before 1991 via the subfrontal craniotomy approach. Since August 1991 almost all pituitary surgery at our institution is done via the trans-sphenoidal route. Between 1991 and 1993 we performed 31 trans-sphenoidal pituitary operations. The patients' medical records, operative reports, and pathological reports were studied. The histological slides of the specimens submitted for rapid intraoperative diagnosis, as well as those submitted for permanent section, were reviewed. All slides of frozen sections, touch preparations, and permanent sections, were stained with haematoxylin and eosin. Additional stains and immunohistochemical studies were performed on the permanent sections only. In addition, the size of the intraoperative specimen as measured by the examining pathologist was recorded for every case. Three cases were excluded from the study. In two cases the diagnosis could not be made intraoperatively and was deferred. Permanent section diagnosis was pituitary adenoma. The specimens submitted for frozen section during a third case were considered non-diagnostic. The patient was eventually found to have a pituitary abscess.

Of the 28 cases of transsphenoidal surgery included in the study, the diagnosis given by frozen section agreed with the permanent section diagnosis in 26 patients. None of the 24 cases of subfrontal craniotomy were excluded from the study. The frozen section diagnosis agreed with the permanent section diagnosis in 22 cases. The table illustrates the cases with discrepancy between frozen section and per-

manent section diagnosis. The accuracy rate for rapid intraoperative diagnosis for the transsphenoidal route was 92.9%. The accuracy rate in subfrontal surgery was 91.7%.

The size of the intraoperative specimen ranged from 0.4×0.4×0.4 cm to 1.2×1.0×0.6 cm in subfrontal surgery, and from 0.1×0.1×0.1 cm to 1.5×0.5×0.1 cm in trans-sphenoidal surgery. Nine trans-sphenoidal samples (32.1%) were smaller than 0.4×0.4×0.4 cm which was the smallest subfrontal sample size. However, both misdiagnosed trans-sphenoidal samples were larger than 0.4×0.4×0.4 cm. All smaller samples were accurately diagnosed.

There are a few studies available in the literature describing frozen section accuracy rates in pituitary surgery. Overall accuracy rates were found to be between 83.1 to 94.3%.^{1-3,6} Lang *et al*¹ emphasised that these rates are consistently lower than accuracy rates of frozen section in other types of surgery⁸ including breast surgery.^{9,10} Farmer *et al*¹¹ reported 91.0% accuracy of frozen section diagnosis in neuropathology. Lang *et al*¹ and other authors indicate that two main factors contribute to lower accuracy rates in pituitary surgery: Firstly, the size of the specimen. They state that extremely small specimens present technical difficulties which result in difficult interpretation. Secondly, the difficult task of histological differentiation between normal pituitary tissue, hyperplasia, and adenoma. Many authors indicate that trans-sphenoidal pituitary surgery provides a limited exposure and therefore results in smaller pieces submitted for intraoperative diagnosis.^{4,5} Therefore, it has been suspected that trans-sphenoidal surgery results in lower frozen section accuracy rates.^{4,5}

The results of our study indicate that the surgical approach did not play a part in determining the accuracy rates. Accuracy rates of frozen section diagnosis were essentially the same for both the trans-sphenoidal and the subfrontal routes. Based on these findings and review of the literature,^{1,2,5} we conclude that problems with the quality of the specimen, as well as problems with histological characteristics of the frozen section, play a more important part than the size of the specimen as reasons for inaccurate diagnosis.

Touch imprint is a very helpful histological technique for intraoperative diagnosis.² It is a very rapid procedure which provides a microscopical sample with less artifacts and with better cellular details. Its disadvantages include some loss of architectural details and the inability to evaluate invasion and margins.¹

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Table 1 Inaccurate intraoperative diagnosis

Approach	Intraoperative diagnosis	Final diagnosis
Trans-sphenoidal	Non-diagnostic	Adenoma
Trans-sphenoidal	Non-diagnostic	Adenoma
Transfrontal	Adenoma	Normal pituitary
Transfrontal	Meningioma	Adenoma

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Bilateral posteroventral pallidotomy for severe antipsychotic induced tardive dyskinesia and dystonia

Tardive dyskinesia as a consequence of long term treatment with antipsychotic drugs has an average prevalence of 15%–20%¹ and may coexist with tardive dystonia which occurs in 1%–4% of patients.² The medical treatment of both is notoriously difficult and it is often impossible to withdraw the provoking medications. We report a patient with early onset severe and refractory tardive dyskinesia and dystonia which was significantly improved by bilateral simultaneous posteroventral pallidotomies.

A 31 year old man had a seven year history of a schizophrenic illness presenting with auditory hallucinations, persecutory delusions, delusions of reference, thought insertion, withdrawal, and broadcasting. There was no history of family psychiatric or neurological disorder and no relevant personal medical or psychiatric history. After initially responding well to treatment with trifluoperazine he discontinued this after a few months and relapsed requiring admission to hospital two years after his first illness. His illness again responded to oral antipsychotic drugs and then depot flupenthixol decanoate (maximum dose of 40 mg monthly). One year later he was first noted to have dyskinetic movements of his mouth and tongue and his depot flupenthixol decanoate was reduced and then discontinued but he quickly relapsed and has required treatment with antipsychotic medication since. His tardive dyskinesia rapidly progressed to involve his limbs and trunk with severe choreiform and hemiballistic movements. Severe dystonia developed involving his neck, larynx, upper limb girdle, and chest. These affected his breathing and swallowing resulting in recurrent chest infections, weight loss, and anaemia. Communication became increasingly difficult because of dysarthria. He was increasingly unable to walk or stand and he had frequent falls with repeated minor injuries necessitating wearing a helmet. Worsening difficulties in managing at home due to intense distress and damage to furniture and sanitary fittings resulted in increasing stays in hospital.

Neurological examination was normal except for the presence of the involuntary

movements. On the modified Obeso dyskinesia scale these were rated as grade 4 mixed chorea and dystonia for all activities,³ and on the Fahn-Marsden dystonia rating scale at 76/120 for movement and 22/30 for disability.⁴ He had a mild normochromic, normocytic anaemia which was only partially responsive to iron supplements but investigations were otherwise normal (brain MRI, EEG, full blood count, urea and electrolytes, glucose, and calcium, thyroid and liver function tests, and serum copper and caeruloplasmin concentrations).

Alternative antipsychotic drugs were tried including sulpiride, remoxipride, risperidone and, for the past two years, clozapine (up to 550 mg/day). In addition the following treatments were tried singly and in combination: sodium valproate (3 g/day), diltiazem (360 mg/day), clonazepam (6 mg/day), tetrabenazine (175 mg/day), vitamin E (1600 IU/day), procyclidine (80 mg/day), benzhexol (16 mg/day) and diazepam (30 mg/day). Salbutamol (16 mg/day), given for a chest infection seemed to bring modest relief. None of the treatments brought about any major or lasting improvement except that high doses of benzodiazepines caused sedation and relief from the movements when he was asleep. He had input from a dietician, speech therapist, and psychologist without success.

After reports of the successful treatment of dopa induced dyskinesias in Parkinson's disease by pallidotomy,⁵ he was referred to the Department of Neurosurgery, Frenchay Hospital, Bristol where he underwent bilateral posteroventral pallidotomy. The day preoperatively he underwent brain MRI on a Philips Gyroscan 1.5 Tesla NT. The detailed anatomy of the basal ganglia was visualised using inversion recovery sequences with long acquisition times to provide high resolution images. The relation between the medial globus pallidus and the anterior and posterior commissures (AC/PC) of the third ventricle were calculated, and the predicted lesion volume defined for each side. A Leksell G frame was secured to the head under general anaesthesia and the patient was transferred to a CT scanner where the coordinates of the AC/PC were established. From these, the target coordinates were transposed to the stereoguide. Through bilateral frontal burr holes a radiofrequency electrode was guided to the target, sequentially on each side. To ensure accurate placement of the proposed lesions, anaesthesia was lightened, so that the patient became partially responsive. Stimulation studies confirmed avoidance of the internal capsule and optic tract. Because of the severity of the involuntary movements it was not possible to use high frequency stimulation to mimic the lesion. Thermal lesions were then made each with a predicted length of 6 mm and diameter of 4 mm.

Postoperative MRI (figure) confirmed accurate placement of the lesions in both posteroventral pallidums. In the immediate postoperative period he was completely free of abnormal movements but his swallowing deteriorated and he developed an aspiration pneumonia. This was successfully treated with a short period of ventilation and antibiotics. One week postoperatively there was a slight return of the orofacial dyskinesia but he was discharged home at 10 days with a sustained improvement in his movement disorder.

At reassessment eight months postoperatively he still had mild to moderate dyskinesia of his mouth and neck with some laryngeal spasm and moderate dystonic movements

resulting in retrocollis. His speech was less dysarthric than preoperatively and he was now able to sit, feed himself, and walk although there had been occasional falls. This was rated as grade 2 on the Obeso scale and 21/120 and 4/30 respectively on the Fahn-Marsden dystonia movement and disability scales. He had gained weight and his anaemia had improved but he had continued to experience psychotic symptoms consisting of auditory hallucinations and delusions of reference although these cause only minor disability. Medication had only been reduced slowly and consisted of benzhexol (12 mg/day), clozapine (400 mg/day), fluvoxamine (100 mg/day), diazepam (6 g/day), iron sulphate (600 mg/day), and salbutamol (16 mg/day). He had had no periods in hospital after the procedure.

This patient presented with tardive dyskinesia of the "buccal-linguomasticatory" type but rapidly progressed to severe tardive dystonia. The picture was consistent with suggested characteristic features of patients with tardive dystonia; male sex, early age of onset after a fairly short duration of antipsychotic treatment, and a high degree of disability.⁶ There is no recognised specific treatment for tardive movement disorders but the patient described here had received

aggressive drug treatment involving strategies described as helpful in case reports including the combination of clozapine and clonazepam recently reported to be helpful in severe cases of tardive dystonia.⁷

Posteroventral pallidotomy is effective in treating both the akinetic and hyperkinetic motor symptoms in Parkinson's disease.⁵ A recent case report described successful use in tardive dyskinesia⁸ but it has not to our knowledge been reported in drug induced tardive dystonia.

The short term outcome in this case has been a significant amelioration of abnormal movements and has arguably been life saving with pronounced improvement in function and quality of life. We suggest that posteroventral pallidotomy should be considered for extremely severe cases of tardive dyskinesia and dystonia but further experience is required to determine its place in the wider treatment of these disorders.

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Figure Postoperative MRI confirming accurate placement of stereotaxic lesions in both posteroventral pallidums.

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CORRESPONDENCE

Pretarsal injections of botulinum toxin improve blephospasm in previously unresponsive patients

The experience of Albanese *et al*¹ is very interesting because it is a good example of the old adage that logical treatment works. The technique as taught by Scott does involve the injection of pretarsal botulinum toxin because it is spasm of the pretarsal muscle that causes the symptoms.

Injection of the preseptal muscle should not be expected to be as effective for controlling the symptom of lid spasm. Injection of the superciliaris is sometimes required to control the brow spasm that many of these patients get.

A similar study to that of Albanese *et al*¹ has been reported locally with a similar result—the logical treatment of the pretarsal muscle is more effective (but produces slightly more side effects) than the less logical injection of the preseptal orbicularis.

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- 1 Albanese A, Bentivoglio AR, Galardi G, Maderna L, Colosimo C, Tonali P. Pretarsal injections of botulinum toxin improve blephospasm in previously unresponsive patients. *J Neurol Neurosurg Psychiatry* 1996;60:693-4.

Albanese replies:

I agree with the propositions of Kowal. In my experience, patients sometimes question the need for pretarsal botulinum toxin injections

due to local pain at the time of treatment. Other side effects (for example, small local haematomas) are a minor concern.

I suspect that, after the pioneering treatments, injection sites have been gradually moved to preseptal and even to orbital locations to avoid local pain. This must be taken into account considering that many patients still do well with preseptal botulinum toxin injections.

ALBERTO ALBANESE

Rehabilitation of gait in Parkinson's disease

We comment on the recent publication by McIntosh *et al*¹ concerning rhythmic auditory motor facilitation of gait patterns in patients with Parkinson's disease. These authors have shown a roughly 10% improvement in gait velocity as a result of entrainment of cadence with a metronome embedded in background music.

Although this study is interesting, the level of improvement in gait is therapeutically small and not directed to the amelioration of the basic deficit in parkinsonian gait. Other studies have clearly shown that the basic deficit in the control of parkinsonian gait is regulation of stride length. Cadence control is intact in Parkinson's disease (Morris *et al*²) and cadence is used as a compensatory mechanism for the defective control of stride length. This is done to increase gait velocity above normal and preset values for each individual patient. We see very little benefit in entraining patients whose cadence is already increased above normal values to improve velocity by values of only the order of 10%. This is particularly so when it is possible to restore normal gait velocity, normal cadence values, and normal stride length by use of either visual cues and more importantly by attentional strategies that are not dependent on any visual cues whatsoever. Under these circumstances it is possible to restore normal gait indices in patients with Parkinson's disease even though they may be totally off their medication or when medication is totally ineffective.

The percentage improvement in gait velocity associated with auditory stimulation is of the same order that can be attained by patients by simply asking them to walk faster. When asked to do so, patients with Parkinson's disease increase their cadence rate, and to a lesser degree stride length, by similar amounts to improve their velocity. This requires no complex equipment—only a gentle prompt to walk at a faster rate.

However, to obtain normal indices patients need to be shown the correct stride length that they are to attain and then told to use attentional strategies to attain that stride length. Again with very minimal equipment and with a modicum of encouragement it is possible to allow patients with festinant gait to walk normally.

We do not disagree with what the authors have demonstrated in their paper, nor do we necessarily disagree with their conclusions; however, we merely wish to put these findings into some form of perspective and of relevance, particularly in the sphere of rehabilitation. We have now used stride length normalisation as a strategy for restoring gait to normal values in our multidisciplinary programme and have found this very effective. The problem is that it requires constant vigilance and continual reinforcement

for it to be applied in a consistent manner. For that reason we have used this approach as a back up for medication failure or medication ineffectiveness and not as a mainstay in treatment.

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- 1 McIntosh GC, Brown SH, Rice RR, Thaut MH. Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;62:22-6.
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Thaut replies:

We entirely concur with Iansek and Morris in regard to the importance of stride length regulation in gait rehabilitation of patients with Parkinson's disease. In regard to their comments about our paper some apparent errors in reading our data may have occurred:

(1) Iansek and Morris state that our study found a 10% increase in velocity. Most of their argument against the rehabilitation relevance of our paper is based on this increase. However, the actual increase in our paper (see p 24) was 36% for ON patients and 25% for OFF patients. This is potentially a very useful increase for rehabilitation.¹

(2) The second argument against the therapeutic usefulness of our paper concerns the improvement of cadence rates which are already raised above normal. Again, this assertion does not fit the cadence rates in our study sample. The cadence for ON patients was 98 and 91 for OFF patients, which is clearly below normal age matched cadence rates and matches gait data from other studies.

(3) The emphasis of Iansek and Morris on the importance of stride length is well taken. However, our study supports that point. Rhythmic cuing improved both stride length and cadence in our study (p 24, table 2, and results section). This dual effect of rhythmic cuing on stride length and cadence in Parkinson's disease has also been reported by other researchers.²

(4) The error of Iansek and Morris in commenting on a 10% increase in velocity may have stemmed from mistaking it for the 10% increase in cadence found in our study. This, however, simply reflects the exact synchronisation to the rhythmic cue which was set only 10% faster than each patient's baseline to avoid hastening into abnormally high step rates. Patients were able to follow the rhythmic cue in close synchronisation without compromising their stride length.

(5) From a clinical perspective it needs to be clearly reiterated that nowhere in this study do we suggest that patients with step rates already above normal should be cued to even higher step frequencies. The assertion of Iansek and Morris in this respect is unfounded. However, patients with Parkinson's disease with slowed step rates may very well benefit from rhythmic cuing to improve velocity, or the entrainment effect may actually be used to decelerate hastened stride. Besides the apparent errors in reading our results, we fail to see how this is less relevant than or contradicts other facilitation