(p 1150). More appropriate advice was given to pharmacists in the *Pharmaceutical Journal* (Dec 3, 1988, p 707) in a letter from the secretary of the professional advisory committee, British Diabetic Association.

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FETAL DOPAMINE-RICH MESENCEPHALIC GRAFTS IN PARKINSON'S DISEASE

SIR,—During the past year clinical trials with grafting of fetal brain tissue into patients with Parkinson's disease have been initiated[1,2] but insufficient information is so far available to evaluate the efficacy of these procedures. Our decision to try neural transplantation in Sweden, in a joint clinical experimental programme also involving centres in the UK and USA, was based on 10 years of research with grafted dopamine neurons in experimental parkinsonism.[3-7] Human-to-rat grafting experiments showed that dopamine neurons from aborted human fetuses of 8–10 weeks survive transplantation and counteract parkinsonian symptoms.[4-6]

Two women, aged 48 and 55, with Parkinson's disease since 1973 and progressively worsening on-off fluctuations for about 8 years spent 60–70% of their waking hours in the "off" phase at the beginning of the study and were in Hoehn and Yahr stage IV–V. During off periods patient 1 had severe hypokinesia with rigidity and tremor. Most often she was unable to walk. Patient 2 had a very disturbed gait during off periods with much impaired balance, rigidity, and hypokinetic movements.

Immunosuppression (cyclosporin, azathioprine, prednisolone) was given from 2 days before transplantation. Ventral mesencephalic tissue from four fetuses (aged 8–10 weeks) was implanted stereotaxically on the side (left in patient 1, right in patient 2) contralateral to that exhibiting the more severe symptoms. Tissue from one fetus was used for each of two implantation sites in the putamen and tissue from two fetuses for one site in the head of the caudate nucleus. (This use of abortion material met the guidelines issued by the Swedish Society of Medicine in 1986.) No postoperative complications were noted. Patient 1 had a short period of fever and a raised leucocyte count 2 weeks after surgery and was treated with antibiotics for 10 days.

The patients have been on the same doses of antiparkinsonian drugs during the 6 months before the transplantation and during the entire postoperative period. Patient 1 takes daily doses of 1200 mg levodopa (combined with benserazide) with 15 mg bromocriptine; patient 2 takes 350 mg levodopa (combined with carbidopa), 15 mg bromocriptine, and 150 mg orphenadrine hydrochloride.

The patients have since 6 months before the operation been keeping a daily log, scoring motor symptoms every 30 min or more frequently. There has been no striking change in the mean time spent "on" during the first 6 postoperative months (for patient 1, preoperative range 31–38%, postoperative 22–44%; for patient 2, preoperative 43–47%, postoperative 45–63%).

We did a battery of timed neurological tests during off periods with the patients on medication. In patient 1 there has been a small but significant bilateral improvement of arm-hand function tests and foot lifting, beginning at about 3 months after transplantation. The improvement has been more marked contralateral to the implanted side. The motor performance of patient 2 has been more variable, but at 6 months she is performing the tests significantly more rapidly on both sides, with no obvious side difference.

The duration of the response to a single dose of 100 mg levodopa showed no major changes 6 months after transplantation. Preoperatively, patient 1 was mobile for 60–75 (mean 64) min and postoperatively for 60–90 (mean 73) min. For patient 2 the duration was 105–120 (mean 111) min preoperatively and 90–120 (mean 108) min postoperatively. However, the magnitude of the levodopa response had increased significantly.

Neurophysiological evaluations seem to support a minor improvement in motor function. The motor readiness potential—a slowly rising negative electroencephalographic potential elicited from 1·5 to 0·5 s before a voluntary movement, has been found to be diminished in patients with Parkinson's disease.[8] From 1–2 months postoperatively this potential gradually increased in both patients during off times. The increase was greater over the transplanted hemisphere before movements of the contralateral hand. In patient 1, this voltage rose from less than 1 μV to 7 μV and from less than 1 μV to 3 μV in patient 2. Both patients showed a significant linear rate of increase postoperatively (general linear model, $p < 0.05$). Patient 2 has shown a significant improvement in arm and hand movements on the side contralateral to transplantation but not ipsilaterally at 6 months postoperatively. In patient 1 the results are not so clearcut but one simple hand movement (squeeze) also improved slightly more contralaterally.

Positron emission tomography (PET) did not reveal any increase in 6-L-[^{18}F]-fluorodopa uptake in the grafted striatum at 6 months after transplanttion.

We conclude that ventral mesencephalic tissue obtained at elective abortions can be implanted into brains of immunosuppressed parkinsonian patients without major complications. However, no improvements of therapeutic value to the patients have been observed up to 6 months postoperatively. The neurophysiological and the clinical test battery changes may indicate a small graft effect. The PET data point to poor survival of the grafted dopamine neurons. This may have been caused by tissue damage at the implantation site (a fairly thick implantation instrument, outer diameter 2·5 mm, was used); by the long interval (5–6 h) between the abortion and implantation; by rejection; or by adverse effects on the grafted neurons from the antiparkinsonain drugs or the disease itself.

Neural transplantation is still an experimental approach, and not a therapeutic alternative, in Parkinson's disease. Several scientific and technical issues need to be clarified in further animal experiments in parallel with the assessment of different grafting procedures in patients.

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WATERBORNE OUTBREAK OF CRYPTOSPORIDIOSIS

SIR,—Despite the fact that *Cryptosporidium* spp have animal reservoir hosts and are transmitted by the faecal-oral route, *Cryptosporidium,* unlike *Giardia duodenalis,* has not yet been acknowledged widely as a significant cause of waterborne gastroenteritis. In 1985, D'Antonio et al[1] described the first waterborne outbreak, in Texas. Rush et al[2] reported *Cryptosporidium* spp oocysts in raw drinking water samples and postulated waterborne spread to account for a peak in cases of cryptosporidiosis in the Sheffield area in 1986. Hayes et al[3] described a waterborne outbreak in Georgia, USA, affecting 13 000 people exposed to a sand-filtered, chlorinated public water supply.

During April, 1988, several cases of cryptosporidiosis were reported to the community medicine specialist in Ayrshire. Extensive epidemiological investigations failed to implicate a common source of food or milk or consistent history of animal contact. Mapping of residences of the affected cases revealed that many of the households concerned received the same public potable water supply. 27 patients either resident in the area served by that supply or who consumed that water were diagnosed as *Cryptosporidium* spp positive (age range 4 months to 93 years), of whom 12 were admitted to hospital (11 required intravenous fluid replacement).

Following notification of the possible involvement of the water supply and the introduction of booster chlorination procedures, the water supply system was thoroughly examined. Twice during the outbreak *Escherichia coli,* coliforms, and faecal streptococci were isolated[4] from a service tank at the treatment works, but all other samples proved negative bacteriologically. *Cryptosporidium* spp oocysts were detected by Wright-Giemsa, modified Ziehl-Neelsen, saffranin/methylene-blue, phenol-auramine, and monoclonal antibody staining in the treated, chlorinated water supply system. Oocysts were present in sludge samples from the treatment works, in the final water leaving one of the service tanks, and in a break-pressure tank delivering chlorinated final water to the supply (range 0·13 to 1000 oocysts/l). Reinspection of the break-pressure tank revealed an old 50 cm fireclay pipe discharging into it; the pipe collecting run-off from the surrounding area. Water samples from the pipe and a nearby stream showed evidence of faecal contamination (244 *E coli,* 403 coliforms, 58 faecal streptococci per 100 ml, and 107 *E coli,* 152 coliforms, 34 faecal streptococci, per 100 ml, respectively). Samples from the stream and soil and grass adjacent to the fireclay pipe were positive for oocysts (0·13 oocyst/l and 32 oocysts/g, respectively). Oocysts were also detected in samples of the treated supply in the absence of faecal bacterial indicators. Following the isolation, drainage and disinfection of the contaminated storage tanks, extensive mains flushing, and emergency booster chlorination, no new cases of waterborne cryptosporidiosis have been reported, and bacteriological and parasitological analyses of subsequent water samples have proved negative.

Oocysts appear to have been introduced via the fireclay pipe into the break-pressure tank which contained final water for distribution rather than by failure of the water treatment process to retain them. There was evidence that cattle slurry had been sprayed on land in the vicinity of the fireclay pipe before the outbreak. *Cryptosporidium* spp oocysts can remain viable for at least 12 months at 4°C[5] and oocyst contamination of final waters in the absence of bacteriological contamination has been reported.[3] Attainable levels of free chlorine following booster chlorination procedures are not oocysticidal.[5] The waterborne route should be considered when clusters of cryptosporidiosis associated with potable water occur, even in the absence of bacterial or viral contamination.

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MISOPROSTOL AND ULCER PROPHYLAXIS

SIR,—From the Dec 3 editorial that accompanied our paper (pp 1293 and 1277) it would appear that our article may not have been written clearly enough. You misunderstand or misinterpret several points we tried to make. I take particular exception to the following views in the editorial: *(a)* that for the most effective ulcer prevention, patients taking NSAIDs should receive both misoprostol (to prevent gastric ulcer) and ranitidine (to prevent duodenal ulcer); *(b)* that duodenal ulcers are apparently unaffected by misoprostol; *(c)* that misoprostol does not relieve the NSAID-related pain; *(d)* that combination therapy would be expected to upset about half as many patients as it would benefit; and *(e)* your reservations about combination therapy for elderly patients.

(a) and *(b)* Your conclusion about combined therapy with ranitidine and misoprostol misinterprets both our study and Ehsanullah's.[1] At least four major studies show that H_2-receptor antagonists do not prevent NSAID-induced gastric ulceration.[1-4] Ehsanullah et al showed that duodenal ulcer was less frequent in patients on ranitidine than in those on placebo and that the duodenal ulcers when present were most likely to occur in those who had pre-existing chronic duodenal ulcer disease. The other studies (including ours) have not found duodenal ulcer to be a common accompaniment of NSAID therapy. Our interpretation is that NSAID therapy may exacerbate pre-existing duodenal ulcer disease. Since the frequency of duodenal ulcer in our placebo group was only 3·6% it would be very difficult to demonstrate significant improvements with misoprostol without a trial of several thousand patients. Although our study was not specifically designed to examine the effect of misoprostol on duodenal ulcer formation, the evidence suggests that misoprostol should prevent both gastric and duodenal ulcers induced by NSAIDs. Therefore, the suggestion that one should choose a particular drug depending upon whether one wished to prevent duodenal or gastric ulcer cannot be supported.

(c) The data show that most patients achieved complete pain relief. Whether this was due to misoprostol could not be ascertained although both misoprostol groups did better than the placebo group in pain relief. The very high placebo response rate precluded a meaningful statistical outcome in this trial despite its size (421 patients).