Neither of the parents concerned were related, nor had they had an affected baby previously. Since all the mothers received multivitamin and iron preparations during pregnancy, our results suggest that genetic factors rather than vitamin deficiency are the cause of the NTD. The high-risk of NTD and its coexistence with other defects in different sexed triplets, together with the unilateral limb defect, support James's suggestions that ovulation induction may be teratogenic, and that subfertility is a risk factor for NTD.

We thank Mrs Ayfer Terazi for her assistance.

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**EXTRA PYRAMIDAL SIGNS IN DEMENTIA OF ALZHEIMER TYPE**

SIR,-We agree with Dr Tyrrell and Dr Rossor (Oct 14, p 920) that differentiating the neurological manifestations of Parkinson's disease from the physical signs of rigidity, akinesia, and lack of facial expression seen in some patients with dementia of the Alzheimer type can be difficult. Tyrrell and Rossor state that dementia-related rigidity does not respond to antiparkinsonian drugs, but our experience differs.

In February, 1988, amantadine prophylaxis was prescribed for the residents of a 235-bed nursing home after symptoms of influenza developed in several patients. Of the 86 patients treated, 8 showed less rigidity and increased sociability following institution of amantadine. In the past 6 months we have cared for 5 other patients with diagnosed dementia who had muscle rigidity when initially evaluated. Each of these patients was given amantadine or levodopa and responded to therapy. In contrast to Tyrrell and Rossor's analysis, the patients who were ambulatory and living at home, ours were bedbound, severely demented, and functionally disabled. A clue that leads us to prescribe antiparkinsonian drugs is the retrospective definition of steep declines in functional abilities leading to admission to our facility. Two case histories illustrate this point.

**Patient 1.**—Diagnosed with dementia five years previously, but end-stage dementia is not rare and responds to treatment with amantadine and/or levodopa. The observation that dementia is complicated by physical debility related to extrapyramidal symptoms that may be responsive to therapy needs further investigation, and clinical trials with antiparkinsonian drugs are indicated. In the meantime doctors should consider carefully monitored drug trials in patients with rigidity and akinesia, whether or not these individuals carry the diagnosis of severe dementia of the Alzheimer type.

**Patient 2.**—Diagnosed with dementia two or three years before admission, and cared for in a local nursing home where bilateral pressure sores developed over her elbows. At admission to our facility she did not talk, was contracted, rigid, and fed with a nasogastric tube. The left elbow pressure sore leaked joint fluid. She responded to treatment with increasing doses of levodopa and amantadine over 9 months. 12 months following admission she was alert, was able to answer simple questions, and fed orally. The patients were assessed by one or both of us for any parkinsonian features.

**NUMBER OF ELDERLY PATIENTS SHOWING FEATURES ASSOCIATED WITH PARKINSON'S DISEASE**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Healthy patients (%)</th>
<th>Day hospital patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty writing</td>
<td>12 (13)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Difficulty turning in bed</td>
<td>8 (9)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Difficulty with buttons</td>
<td>6 (7)</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Reduced absent arm swing</td>
<td>34 (37)</td>
<td>36 (76)</td>
</tr>
<tr>
<td>Reduced stride length</td>
<td>7 (8)</td>
<td>37 (74)</td>
</tr>
<tr>
<td>Tremor</td>
<td>10 (11)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Increased tone</td>
<td>2 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cogwheel rigidity</td>
<td>0</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Facies</td>
<td>2 (2)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Speech</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Dysdiadochokinesis</td>
<td>0</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Start hesitation</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total with 1 or more features</td>
<td>43 (47)</td>
<td>49 (98)</td>
</tr>
</tbody>
</table>

The table gives details of the features associated with Parkinson's disease in these patients. Almost half the healthy elderly and almost all of the day hospital patients had at least one feature of Parkinson's disease. Thus, elderly people in general often have features of Parkinson's disease. This finding emphasises the importance of reviewing the response to levodopa therapy in elderly subjects diagnosed as having Parkinson's disease to avoid unnecessary prescription of this potentially toxic agent.

**AMINOACID ISOMERISATION AND MICROWAVE EXPOSURE**

SIR,—Microwaves are used for cooking and for scientific purposes. One application is the hydrolysis of peptides and proteins. To see if such hydrolysis alters amino acids by isomerisation or degradation we did the following study on three different milk formulae.

Formulæ were tested in their native state, hydrolysed conventionally by 6 mol/l hydrochloric acid at 105°C for 16 h, heated for 10 min in a microwave oven used for heating of infant food or heated to 80°C in a water bath for the same period.

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4 and 3 trans-hydroxyproline and 3 and 4 cis-hydroxyproline were measured by thin-layer chromatography. The results were checked by gas chromatography and mass spectrometry and by high pressure liquid chromatography (HPLC). The same samples were also studied by HPLC with 'Cyclodextrin B' beta-cyclodextrin columns to obtain D and L amino acid separation. As marker, D-proline was used.

Free aminoisooxazoles in milk formulae, conventionally hydrolysed milk samples and conventionally heated milk samples did not contain cis-3 or cis-4 hydroxyproline. However, all three formulae contained cis stereoisomers of hydroxyproline after microwave treatment and the microwave treated samples were the only specimens in which D-proline was found on HPLC; concentrations of cis-isomers were 1–2 mg/l.

The conversion of trans to cis forms could be hazardous because when cis-aminoisooxazoles are incorporated into peptides and proteins instead of their trans isomers this can lead to structural, functional, and immunological changes. We therefore advise further studies on the molecular changes of aminoisooxazoles and other compounds because so little has been published about this aspect of microwave treatment.

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RECURRENT MELANOMA AFTER TOPICAL TRETINOIN

Sir,—In some countries, including Australia, topical tretinoin (all-trans-retinoic acid) is readily available as a non-prescription item. Its use has increased in the wake of reports in the medical and lay press that these agents have anti-aging and anti-cancer effects. We have seen a cutaneous melanoma developing at the site of a pigmented lesion previously treated with tretinoin cream.

A 58-year-old man presented to the Sydney melanoma unit in July, 1989, with a black pigmented nodule affecting the right preauricular skin. A brown macule had been present at that site for the preceding 3 years and in November, 1988, the patient had purchased a 20 g tube of 'Retin-A' 0.05% tretinoin cream, having been prompted to do this by a newspaper article that suggested that malignant tumour progression could be "stopped cold" by such a preparation. He treated the lesion with 10 g tretinoin over the ensuing two months. By late December, 1988, the macule had regressed completely. 3 weeks later, however, a black "pimple-like" spot appeared at the site of the original lesion, and this new lesion had enlarged until July, 1989, when he sought medical attention.

The nodule was excised and was confirmed to be a 7 mm melanoma. An intraepidermal component was lacking and there were several mitotic figures in the dermis. The area was widely excised and a superficial parotidectomy and modified radical neck dissection were performed. No residual tumour was identified in any of the 42 lymph nodes removed. Total cutaneous examination failed to reveal any other site which may have given rise to the tumour, and visceral disease was not detected. The patient has remained disease-free for the past 4 months.

There is some evidence to support the evaluation of topical retinoids in the treatment of melanoma. These agents inhibit the proliferation of transformed melanoma cell lines in vitro and transplanted melanoma tumours in vivo. Complete regression of multiple cutaneous metastatic lesions has been documented in one melanoma patient after the topical application of tretinoin cream. However, the lay press occasionally reports scientific information in a way that is subject to misinterpretation. This contributed to our patient's delay in seeking medical advice. Survival in melanoma is directly related to tumour thickness; less than 25% of patients with tumours greater than 4 mm in thickness survive beyond 10 years. It could be argued that our patient had a cutaneous metastasis and not a primary lesion. However, since he had a pigmented lesion that regressed after tretinoin therapy at the same location and had no evidence of cutaneous or visceral disease elsewhere, it is much more likely that this tumour was a primary lesion. Histological examination revealed a nodular melanoma lacking an intraepidermal component, suggesting that the retinoid destroyed the upper component of the tumour but was incapable of penetrating deeper layers of skin. This effect may be similar to that seen with topical 5-fluorouracil, and the anti-venereal retinoid is used to treat invasive basal or squamous cell carcinomas.

This case illustrates a potential adverse consequence of inappropriate and unsupervised use of tretinoin preparations, and suggests that this drug should be dispensed only by prescription. Until more information is available on the biological effects of these agents we contend that topical retinoid preparations should not be used to treat pigmented lesions of the skin, except under direct medical supervision.