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been shown to be associated with the thermolabile phenotype.1 Neugebauer and colleagues (Feb 15, p 473)2 report a significantly higher prevalence of the modified allele in diabetic patients with retinopathy, but did not assess whether this association is mediated by plasma concentrations of homocysteine. We report on the association between moderate hyperhomocysteinaemia and retinopathy in 25 consecutive patients with insulin-dependent diabetes (WHO criteria) aged 35—59 years who had had diabetes for at least 10 years. We measured plasma concentrations of homocysteine by a previously described method.3 Retinopathy was assessed by fundus photography according to the EURODIAB protocol;4 the observer was unaware of biochemical data. Significant differences between frequencies were tested by Fisher’s exact test. 12 patients had retinopathy and 13 did not. None of the patients had clinical or biochemical signs of kidney disease. Moderate hyperhomocysteinaemia—plasma concentration of homocysteine above 10 μmol/L, which corresponds to the 90th percentile of the distribution of a non-diabetic population of similar age—was significantly more common in patients who had retinopathy than in those who did not (p<0.03, table). This finding accords with that of Neugebauer and colleagues and suggests that moderate hyperhomocysteinaemia is associated with diabetic retinopathy and represents a link between this condition and the mutation in the MTHFR gene.

An increase in plasma homocysteine of the same magnitude as that seen in the patients with diabetic retinopathy is associated with increased cardiovascular risk in individuals who do not have diabetes.5 Hyperhomocysteinaemia may accelerate cell injury and platelet-mediated intimal proliferation of smooth muscle cells which lead to enhanced atherogenesis. Cell injury at the level of the small vessels may also contribute to the development of diabetic retinopathy. In patients with insulin-dependent diabetes, the major cardiovascular risk factors do not explain the excess cardiovascular morbidity and mortality. Conversely, 1 half of the heart and legs is associated with clinical signs of microangiopathy, such as retinopathy and kidney disease. Thus, moderate hyperhomocysteinaemia may represent a mechanism that accounts for the concomitant presence of the two conditions in patients with insulin-dependent diabetes.

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Hormone replacement therapy and high incidence of breast cancer between mammographic screens

Sir—Several research groups have found that the interval cancer rate—ie, the incidence of breast cancer in the interval between mammographic screens, is higher in the NHS Breast Screening Programme than had been expected from the findings of the Swedish two county trial of mammographic screening.1,2 Threlfall and colleagues (Feb 15, p 472)2 now report that the interval cancer rate is comparatively higher among women aged 50—59 than among those aged 60—64 at screening. One factor that needs to be considered is that the use of hormone replacement therapy by women screened in the UK may contribute to this relatively high rate of interval cancer. Randomisation for the Swedish trial was done in 1977—80, when use of hormone replacement therapy was rare, whereas among women in the NHS Breast Screening Programme, the prevalence of use of hormone replacement therapy was about 15% in 1990 and 30% in 1995 (unpublished observations), and was twice as frequent among women aged 50—59 years than among those aged 60—64 years.3

Use of hormone replacement therapy at the time of screening increases the mammographic density of breast tissue. Laya and colleagues’ study—only the study of which we are aware that looked at interval cancers in relation to the use of hormone replacement therapy—suggests that its use lowers the chance of a woman having her cancer detected at screening, thereby increasing the rate of interval cancer. They reported that compared with never-users of hormone replacement therapy, the relative risk of having an interval cancer diagnosed in the first year of mammography as opposed to a screen-detected cancer was 5·2 for current users of hormone replacement therapy and 1·1 for former users.4 However, these findings are based on only seven women with interval cancer and the study was conducted in the USA where annual screening is common, so no data were presented for cancers diagnosed beyond the first year after screening. Nevertheless, if correct, and if the effect of hormone replacement therapy on interval cancers persists for 2 years, these results indicate that among women screened in the UK in 1990, about 700 extra interval cancers would have been detected if users of hormone replacement therapy. This excess is sufficient to account for the higher than expected rate of interval cancer in the NHS Screening Programme as a whole, including the higher rate among women aged 50—59 than among those aged 60—64. Moreover, quite apart from its effect on mammography, any increase in the background incidence of breast cancer due to use of hormone replacement therapy would also increase the number of interval cancers diagnosed. With the large and increasing number of women who are users of hormone replacement therapy, it is important to know the extent to which this therapy contributes to the high rate of interval cancer seen in the NHS Breast Screening Programme. The available evidence is too uncertain to guide policy. However, if current use but not former use, of hormone replacement therapy lowers the efficacy of screening, there might be a simple way to reduce the rate of

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A research culture that asks too much

Sir—As a practising clinician with an interest in forensic medicine I am all too aware that medicine in the UK has all but been destroyed by a research culture that has demanded and been given far too much, both in resources and influence, as you point out in your Feb 22 editorial. The impossible has always been demanded of the academic clinician and it has always resulted in the same response, a neglect of teaching duties in favour of attendance at conferences or committees by senior researchers, whereas the more junior doctors to whom the task has been delegated remain in the research laboratory. The emphasis on research is producing dangerously inept clinicians and surgeons. Spending large chunks of one's early career focused on a tiny area of medicine inevitably reduces the time available for gaining the broad knowledge and experience necessary to the practising doctor. In 1974, as a newly qualified doctor, I was already shocked by the narrowness of the competence of newly appointed consultants. They seemed to be one-disease men, visibly floundering out of their depth when fairly common conditions outside their field inconveniently appeared in their patients. Now this failing is sadly reflected in my forensic experience: patients admitted to general hospitals with common conditions are not being diagnosed or adequately treated. Patients are being asked to pay too high a price for the development of their doctors' critical faculty.

It is a myth that all doctors must spend time in academic research in order to become good clinicians and competent surgeons. In my experience: most young people go into medicine with the aim of treating patients. Only

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### Table: Interval since screening by age-group

<table>
<thead>
<tr>
<th>Interval since screening by age-group</th>
<th>Observed cases</th>
<th>Expected cases</th>
<th>Observed/expected rate</th>
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</thead>
<tbody>
<tr>
<td>49 years (n=9206)</td>
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<td></td>
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<tr>
<td>0-11 months</td>
<td>7</td>
<td>10-3</td>
<td>0-68</td>
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<tr>
<td>12-23 months</td>
<td>9</td>
<td>7-8</td>
<td>1-16</td>
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<tr>
<td>Total</td>
<td>16</td>
<td>18-0</td>
<td>0-89</td>
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<tr>
<td>50-54 years (n=25164)</td>
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<td></td>
<td></td>
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<tr>
<td>0-11 months</td>
<td>21</td>
<td>40-2</td>
<td>0-52</td>
</tr>
<tr>
<td>12-23 months</td>
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<td>34-3</td>
<td>0-64</td>
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<tr>
<td>Total</td>
<td>43</td>
<td>74-6</td>
<td>0-58</td>
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<tr>
<td>55-59 years (n=20326)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0-11 months</td>
<td>11</td>
<td>33-5</td>
<td>0-29</td>
</tr>
<tr>
<td>12-23 months</td>
<td>25</td>
<td>34-1</td>
<td>0-73</td>
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<tr>
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<td>0-50</td>
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<td>60-64 years (n=19251)</td>
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<td>0-11 months</td>
<td>11</td>
<td>40-3</td>
<td>0-27</td>
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<tr>
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<tr>
<td>Total</td>
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<td>65-69 years (n=17789)</td>
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<td>0-14</td>
</tr>
<tr>
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<td>0-50</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>70-6</td>
<td>0-31</td>
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</table>

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