Monoclonal antibodies that target T cells have shown some benefit in rheumatoid arthritis although responses have not been long lasting. This is partly due to insufficient therapy consequent upon antibody immunogenicity. Use of humanised antibodies, which are expected to be less foreign to man than conventional rodent antibodies, might overcome this problem. We therefore assessed in a phase 1 open study the potential of a "lymphocyte depleting" regimen of the humanised monoclonal antibody CAMPATH-1H in 8 patients with refractory rheumatoid arthritis.

Apart from symptoms associated with first infusions of antibody, adverse effects were negligible. Significant clinical benefit was seen in 7 patients, lasting for eight months in 1. After one course of therapy, there was no measurable antoglobulin response, although 3 out of 4 patients have become sensitised on retreatment.

Humanisation reduces the immunogenicity of rodent antibodies but anti-idiotypic responses may still be seen on repeated therapy, even in patients sharing immunoglobulin allotype with the humanised antibody.

**Introduction**

Monoclonal antibodies (mAbs) are being studied for treatment of autoimmune and inflammatory diseases. Rheumatoid arthritis is a common, progressive, crippling disease; because of its association with HLA, and the response to therapies such as thoracic duct drainage, total lymphoid irradiation, and cyclosporin, there is compelling evidence that T cells have a crucial role in its pathogenesis. Although mAbs that target T cells have shown benefit in rheumatoid arthritis, responses have been of limited duration. Furthermore, the therapeutic "window" within which antibodies could be used has been narrow because of the antoglobulin response against the therapeutic agent.

**Patients and methods**

Patients

Characteristics of the 8 patients are shown in table 1. They fulfilled the American Rheumatism Association criteria for rheumatoid arthritis and had active disease as defined by three of the following four criteria: Ritchie articular index > 10, early morning stiffness > 45 min, erythrocyte sedimentation rate (ESR) > 30 mm per hour, joint score > 10. 7 patients were seropositive. Their disease had proved unresponsive to a current and at least one other second-line agent, and these had been stopped at least four weeks before administration of CAMPATH-1H. Patients were allowed to continue with non-steroidal anti-inflammatory drugs (NSAIDs) and an existing dose of prednisolone (up to 20 mg daily). They were otherwise healthy, and had normal renal and hepatic function. Approval of the local ethics committee and informed consent of the patients were obtained.

**Treatment**

CAMPATH-1H—CAMPATH-1H is a human IgG1 mAb that is specific for the glycoprotein CDw52, an antigen present on all lymphocytes and some monocytes. This mAb was derived by humanisation of the rodent antibody CAMPATH-1G.

Therapeutic-grade antibody was produced in Chinese hamster ovary cells grown in a hollow-fibre continuous culture system (Acusyst-Junior, Endotronics Inc, Minneapolis, MN, USA) and was purified on protein A. The antibody was formulated in (Acusyst-Junior, Endotronics Inc, Minneapolis, MN, USA) and (Acusyst-Junior, Endotronics Inc, Minneapolis, MN, USA) and was purified on protein A. The antibody was formulated in

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Disease Duration (y)</th>
<th>Baseline ESR (mm/h)</th>
<th>Baseline CRP (mg/L)</th>
<th>Baseline DAS28</th>
<th>Baseline Ritchie Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>10</td>
<td>30</td>
<td>4</td>
<td>3.1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>F</td>
<td>15</td>
<td>25</td>
<td>3</td>
<td>3.5</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>20</td>
<td>35</td>
<td>5</td>
<td>3.8</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>10</td>
<td>40</td>
<td>6</td>
<td>3.2</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>15</td>
<td>20</td>
<td>2</td>
<td>3.6</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>25</td>
<td>30</td>
<td>4</td>
<td>3.8</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>F</td>
<td>12</td>
<td>25</td>
<td>3</td>
<td>3.4</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>M</td>
<td>18</td>
<td>35</td>
<td>5</td>
<td>3.9</td>
<td>17</td>
</tr>
</tbody>
</table>

**Humanised monoclonal antibody therapy for rheumatoid arthritis**

**JOHN D. ISAACS**  **RICHARD A. WATTS**  **BRIAN L. HAZLEMAN**  **GEOFF HALE**  **MARY T. KEOGAN**  **STEVE P. COBBOLD**  **HERMAN WALDMANN**

To reduce to a minimum the immunogenicity of therapeutic antibodies, "reshaping" by genetic engineering has been used to convert rodent antibodies to a human form. Such "humanised" antibodies should appear less foreign to man than do conventional rodent antibodies. With existing techniques, however, "humanisation" leaves open the chance for anti-idiotypic and anti-allotypic responses. We have assessed the potential of humanised antibodies for treatment of rheumatoid arthritis.

**ADDRESSES**

Cambridge University Department of Pathology (Immunology Division), Tennis Court Road, Cambridge CB2 1QF, UK (J. D. Isaacs, MRCP, G. Hale, PhD, S. P. Cobbold, PhD, H. Waldmann, MRCP), and Departments of Rheumatology (R. A. Watts, MRCP, B. L. Hazleman, FRCP), and Clinical Immunology (M. T. Keogan, MRCP). Correspondence to Dr John D. Isaacs.
phosphate-buffered saline and after sterility and endotoxin checks it was stored at −30°C before administration. Before infusion it was diluted in 100 ml (first treatment) or 500 ml (retreatment) normal saline.

**Therapeutic regimen—**Patients were admitted to hospital for antibody therapy. CAMPATH-1H was given by intravenous infusion over 2–4 hours, during which vital signs were recorded every 15 min. A course of therapy lasted for 10 days, and consisted of 4 mg antibody daily for 5 days followed by 8 mg antibody daily for 5 days. Between daily infusions, patients were fully mobile but did not receive physiotherapy. A second course of therapy consisted of 40 mg antibody daily for 5 days.

**Assessment**

Ritchie articular index and joint score were assessed immediately before treatment, and daily during treatment. Duration of morning stiffness, patient’s global assessment (sum of 4 scores representing night pain, rest pain, general wellbeing, and functional ability), each measured on a visual analogue scale (max=100 each) were recorded. A similar assessment was done every week before treatment, and daily during treatment. Duration of morning stiffness, patient’s global assessment (sum of 4 scores representing night pain, rest pain, general wellbeing, and functional ability), and rheumatoid factors; an additional advantage is that it discriminates between anti-idiotype, anti-isotype, and anti-allotype antiglobulins. This assay could detect 10 ng/ml monoclonal antiglobulins. This test is a sensitive and functional measure of antiglobulin neutralising activity, this assay was used to determine absolute concentrations in the sera. The sensitivity of the assay was between 40 and 100 ng/ml.

**Antiglobulin response—**Two assays were used to assess antiglobulin reactivity in patients’ sera. Serum samples from all patients were tested in a double-capture enzyme-linked immunosorbent assay (ELISA). This test is a sensitive and specific assay for detecting antiglobulins able to bind monovalently to CAMPATH-1H, thereby excluding low-affinity antiglobulins and rheumatoid factors; an additional advantage is that it discriminates between anti-idiotype, anti-isotype, and anti-allotype antiglobulins. This assay could detect 10 ng/ml monoclonal anti-CAMPATH-1 idiotype antibody (YID 13-9), YID 13-9, and 2 µg/ml polyclonal goat anti-human IgG (Fc-specific, Sigma 12136). Sera that were positive in the ELISA were further analysed with a functional read-out that measured their ability to block binding of CAMPATH-1H to the CAMPATH-1 antigen. 25 µl heat-inactivated serum was mixed with an equal volume of CAMPATH-1H (4 µg/ml in heat-inactivated normal human serum). 5 × 10^6 peripheral blood lymphocytes were then added and bound CAMPATH-1H was sought. Blocking activity was expressed as the serum titre that inhibited CAMPATH-1H binding by 50%. This was equivalent to 125 ng/ml YID 13-9. While providing a functional measure of antiglobulin neutralising activity, this assay may not be completely specific. For example, soluble CAMPATH-1 antigen also inhibits in this assay (unpublished).

**TABLE I—PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Patient, age (yr)</th>
<th>Disease duration (yr)</th>
<th>ESR (mm/h)</th>
<th>CRP (mg/l)</th>
<th>Ritchie*</th>
<th>Joint score*</th>
<th>Morning stiffness (min)</th>
<th>Global assessment</th>
<th>Rheumatoid factor (IU/ml)</th>
<th>Previous therapy</th>
<th>Prednisolone (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, 32</td>
<td>2</td>
<td>100</td>
<td>160</td>
<td>10</td>
<td>17</td>
<td>30</td>
<td>181</td>
<td>40</td>
<td>G, P, M, S</td>
<td>7-5</td>
</tr>
<tr>
<td>B, 62</td>
<td>13</td>
<td>95</td>
<td>45</td>
<td>34</td>
<td>15</td>
<td>300</td>
<td>286</td>
<td>2112</td>
<td>G, P, M, S, yIFN</td>
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</tr>
<tr>
<td>C, 69</td>
<td>9</td>
<td>64</td>
<td>112</td>
<td>36</td>
<td>16</td>
<td>120</td>
<td>212</td>
<td>0</td>
<td>G, P, M, S, A, CyA</td>
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</tr>
<tr>
<td>D, 46</td>
<td>16</td>
<td>48</td>
<td>45</td>
<td>22</td>
<td>12</td>
<td>45</td>
<td>105</td>
<td>125</td>
<td>G, P, M, S</td>
<td>7-5</td>
</tr>
<tr>
<td>E, 50</td>
<td>19</td>
<td>55</td>
<td>94</td>
<td>38</td>
<td>18</td>
<td>300</td>
<td>284</td>
<td>121</td>
<td>G, P, S, C</td>
<td>20-0</td>
</tr>
<tr>
<td>F, 61</td>
<td>35</td>
<td>40</td>
<td>90</td>
<td>34</td>
<td>11</td>
<td>5</td>
<td>299</td>
<td>56</td>
<td>G, P, S, CyA</td>
<td>0</td>
</tr>
<tr>
<td>H, 68</td>
<td>3</td>
<td>80</td>
<td>128</td>
<td>27</td>
<td>12</td>
<td>60</td>
<td>175</td>
<td>233</td>
<td>S, Romazoin</td>
<td>0</td>
</tr>
</tbody>
</table>

*Maximum attainable Ritchie and joint scores were 78 and 26, respectively. 15% of 4 scores (max = 100 each) measured on a 10 cm visual analogue scale representing night pain, rest pain, general wellbeing, and functional ability. ESR = erythrocyte sedimentation rate. CRP = C-reactive protein. G = gold, P = penicillamine, M = methotrexate, S = sulphasalazine, yIFN = y-interferon, A = azathoprine, CyA = cyclosporin, C = cyclophosphamide.

**Fig 1—Lymphocyte subset counts.**

n refers to no of patients analysed at each time point (subset data could not be obtained when total lymphocyte count < 0.4 × 10^9/l, and pre-treatment values not available for patient E). Horizontal line represents lower limit of normal range for total lymphocyte count.

**CAMPATH-1H—**Serum CAMPATH-1H concentrations were measured by immunofluorescence with human peripheral blood lymphocytes. 5 × 10^6 cells (suspended in wash buffer [phosphate buffered saline containing 0.2% bovine serum albumin and 0.01% azide]) were incubated for 1 h on ice with an equal volume of patient serum (heat-inactivated at 56°C for 30 min). After extensive washing, bound CAMPATH-1H was sought with fluorescein-isothiocyanate-conjugated monoclonal anti-human IgG, immunoglobulin (Sigma F0767 [Poole, Dorset, UK] diluted 1/100 in wash buffer containing 10% heat-inactivated normal rabbit serum). Cells were fixed, and relative fluorescence intensity was measured by means of a FACScan (Becton Dickinson). A standard curve of median fluorescence values obtained with known concentrations of CAMPATH-1H (diluted in heat-inactivated normal human serum) was used to determine absolute concentrations in the sera. The sensitivity of the assay was between 40 and 100 ng/ml.

**Clinical findings**

The first infusion of antibody led to a rapid fall in total lymphocyte count in all patients. Lymphopenia was evident as early as an hour after the start of the first infusion, when systemic symptoms of fever (up to 40°C), rigors, and nausea developed in all patients; hypotension developed in 1 patient. These symptoms lasted for 2–3 hours and were more pronounced in patients receiving 40 mg of antibody at
TABLE II—CLINICAL OUTCOME AFTER A SINGLE COURSE OF TREATMENT

<table>
<thead>
<tr>
<th>Index</th>
<th>Day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritchie</td>
<td>34 (10–39)</td>
</tr>
<tr>
<td>Joint score</td>
<td>16 (12–18)</td>
</tr>
<tr>
<td>Morning stiffness (min)</td>
<td>90 (3–360)</td>
</tr>
<tr>
<td>Global score</td>
<td>90 (3–360)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>58 (40–100)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>103 (45–160)</td>
</tr>
</tbody>
</table>

Values are median (range) for each index at each time point. *Number in square brackets refers to patients remaining in study at each time point. †Significant at p < 0.05 by Mann-Whitney U test.

TABLE III—SEROLOGICAL AND CLINICAL RESPONSES TO CAMPATH-1H THERAPY

<table>
<thead>
<tr>
<th>Patient</th>
<th>After first treatment</th>
<th>Blocking activity†</th>
<th>Duration of response (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After treatment</td>
<td></td>
<td>First</td>
</tr>
<tr>
<td>A</td>
<td>&lt;0.01</td>
<td>&lt;1/4</td>
<td>1/64</td>
</tr>
<tr>
<td>B</td>
<td>&lt;0.01</td>
<td>5.0</td>
<td>1/8</td>
</tr>
<tr>
<td>C</td>
<td>&lt;0.01</td>
<td>&lt;1/4</td>
<td>&lt;1/4</td>
</tr>
<tr>
<td>D</td>
<td>&lt;0.01</td>
<td>25.0</td>
<td>1/16</td>
</tr>
<tr>
<td>E</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>1/4</td>
</tr>
<tr>
<td>F</td>
<td>&lt;0.01</td>
<td>&lt;1/4</td>
<td>&lt;1/4</td>
</tr>
<tr>
<td>G</td>
<td>&lt;0.01</td>
<td>&lt;1/4</td>
<td>1/4</td>
</tr>
<tr>
<td>H</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;1/4</td>
</tr>
</tbody>
</table>

As measured by ELISA, and expressed in ng/ml equivalents of the monoclonal anti-idiotype YID 13.9, which recognizes the CAMPATH-1H idiotype.

Blocking activity refers to the ability of patients' sera to inhibit by 50% the binding of 2 µg/ml CAMPATH-1H to antigen on PBL, this is equivalent to approximately 125 ng/ml of the monoclonal anti-idiotype antibody YID 13.9.

LABORATORY FINDINGS

Allotyping—The immunoglobulin allotypes are shown in table IV. Despite the small number of patients, these data accord with other published results. In particular, the Glm 1, 2, 3, 17 allotype has been shown to be more common and the Glm 1, 3, 17 less common in patients with rheumatoid arthritis. CAMPATH-1H has the allotype Glm 1, 17, Km3. All our patients possessed the Km3 light-chain allotype but at least 2 differed in heavy-chain allotype from CAMPATH-1H and therefore had the potential to make an anti-allotype response. It was not possible to achieve a consistent assessment of Glm 1, 2, or 17 allotype for patients B and F, possibly because of rheumatoid factors interfering with the haemagglutination inhibition assay.

CAMPATH-1H—Trough antibody concentrations remained below 1 µg/ml in all patients (fig 2) until dose escalation when they reached between 1 and 5 µg/ml. The mean value 24 hours after the last dose of antibody was about 2.3 µg/ml. Antibody concentrations fell with a half-life of less than a week, so that 2 weeks after therapy, antibody was undetectable in all but 2 patients (F, G), in whom antibody concentrations were 40 ng/ml at 25 days and 80 ng/ml at 19 days, respectively. It should be noted that about 10 µg/ml of CAMPATH-1H is needed to saturate surface receptors (CDw52) on peripheral blood lymphocytes in vitro. In all patients completing a second course of treatment trough antibody values reached at least 5 µg/ml during therapy (fig 2).
binding of CAMPATH-1H to its antigen. We cannot
after one course of therapy but 3 out of 4 retreated patients
humanised mAb treatment for rheumatoid arthritis. We
developed antiglobulins and these were able to inhibit the
were unable to detect a significant antiglobulin response
factors).
CAMPATH-1H antigen or an effect of rheumatoid
may not represent specific antiglobulins but perhaps soluble
activity could be detected even before therapy (and therefore
from these and a further 2 patients also showed much weaker
lymphocytes as predicted. Unexpectedly, however, sera
assay, sera from these 3 patients were able to inhibit the
presence of a non-idiotype component in this patient’s
serum suggests an allotype mismatch. In the functional
was not possible to allotype patient B reliably, and the
they shared heavy-chain allotype with CAMPATH-1H. It
retreatment. 2 of these had a pure anti-idiotype response and
(B, D, E) developed antiglobulins 6–10 days after the end of
2 of these had a pure anti-idiotype response and
they shared heavy-chain allotype with CAMPATH-1H. It
was not possible to allotype patient B reliably, and the
presence of a non-idiotype component in this patient’s
serum suggests an allotype mismatch. In the functional
assay, sera from these 3 patients were able to inhibit the binding of CAMPATH-1H to human peripheral blood lymphocytes as predicted. Unexpectedly, however, sera from these and a further 2 patients also showed much weaker blocking activity 6–15 days after the first course of therapy. This may represent a weak primary antiglobulin response. However, it should be noted that in 2 of these patients weak activity could be detected even before therapy (and therefore may not represent specific antiglobulins but perhaps soluble CAMPATH-1H antigen or an effect of rheumatoid factors).

**Discussion**

To our knowledge this study is the first assessment of humanised mAb treatment for rheumatoid arthritis. We were unable to detect a significant antiglobulin response after one course of therapy but 3 out of 4 retreated patients developed antiglobulins and these were able to inhibit the binding of CAMPATH-1H to its antigen. We cannot conclude from these results whether an allotype mismatch increases the likelihood of an antiglobulin response to CAMPATH-1H, but it is now clear that even in the best possible situation of allotype matching, an anti-idiotype response may still be elicited. This finding accords with predictions from animal experiments.\(^{10,31}\) Our data agree with experience of rat mAb CAMPATH-1G treatment for resistant rejection in transplant recipients.\(^ {12}\) With an equivalent assay to ours, an antiglobulin response was detected in 11 of 14 patients, between 11 and 18 days after a single course of mAb therapy, even with concurrent immunosuppression, which generally reduces the incidence of antiglobulin responses. In that transplant study patients received 5–10 mg/day of CAMPATH-1G for 6–10 days and most patients mounted a mixed (anti-isotype and anti-idiotype) antiglobulin response.

The identity of the blocking activity detected in some sera before and after one course of treatment in our study is unclear; it may represent a soluble form of the CAMPATH-1 antigen or perhaps low affinity antiglobulins, but discriminating between these options is difficult in view of the low titres. Whatever the nature of this blocking activity, effective serum antibody values and a sustained therapeutic response were seen upon re-treatment.

The side-effects observed in this study were acceptable. The first-dose response accompanied lympholysis and was presumably mediated by released cytokines. Similar symptoms are seen in patients receiving OKT3, a mAb directed to CD3 epsilon chain on human T cells. In that setting, cytokines are released as a result of T-cell activation, and a combination of tumour necrosis factor alpha and interleukin-1 can account for the clinical findings.\(^ {19}\) Apart from occasional oral ulceration infective complications were not seen in our patients. This observation mirrors that in laboratory animals, which stay healthy despite many weeks of anti-T cell antibody therapy, perhaps because of normal levels of neutrophils and monocytes. Infective complications, including herpes simplex infection, have been reported during antibody therapy but usually in association with additional potent immunosuppression.\(^ {14,45}\)

Animal experiments conducted in our own laboratories suggest that it may eventually be possible to control autoimmune states with single courses of antibody therapy by inducing tolerance to the putative autoantigen.\(^ {16}\) However, until appropriate regimens are available for human therapy, inflammation must be controlled by alternative means; antibodies seem to be the most potent agents available. Already they have been used to treat otherwise refractory cases of psoriasis\(^ {17}\) and inflammatory bowel disease,\(^ {18}\) and our study extends our knowledge of their use in rheumatoid arthritis. Although the improvements we observed were generally modest, it is remarkable that they were obtained with such small doses of antibody. To maximise our chance of targeting most peripheral lymphocytes, we doubled the dose of CAMPATH-1H administered after day 5 but serum concentrations were still below those required to saturate peripheral blood lymphocytes. Future studies must take advantage of the potent effects of CAMPATH-1H, whilst investigating ways of maximising therapeutic benefit. Our current re-treatment protocol is designed to ask whether a higher dose of mAb will improve outcome, and preliminary data are encouraging; 2 of 3 evaluable patients have now achieved an increased response duration on re-treatment. Alternatively, additional benefit may derive from combination therapy. Thus sequential treatment with CAMPATH-1H and a CD4 mAb gave a longer-lasting
remission (> 3 years) than did CAMPATH-1H alone in a patient with vasculitis (ref 19 and M. Lockwood, personal communication), suggesting that this combination can induce tolerance. It is also possible that CAMPATH-1H will prove less immunogenic when administered in higher doses. Thus, mice do not make an antiglobulin response against CD4 mAbs provided a dose above a critical minimum is given.20

The variation in clinical response that we recorded may reflect the complex pathogenesis of rheumatoid arthritis. One hypothesis is that monocytes are the cell type that ultimately bring about the tissue damage seen in late disease,21 but all the data from studies using mAbs and other T-cell targeted therapies suggest that, if this hypothesis is true, they must be driven by self-reactive T cells. The rapid improvements seen in our patients point to an inflammatory role for T cells in late disease. By contrast, the lack of impact on ESR and C-reactive protein concentrations suggests that in rheumatoid arthritis the acute-phase response is driven by monocyte-derived cytokines.22 Use of a two-tiered approach that targets both T cells and monocytes may be the ultimate requirement. The reduced immunogenicity of CAMPATH-1H compared with rodent antibodies and the consequent ability to retreat patients with higher doses or with other mAbs, will enable us to learn how to use mAbs to their best advantage both in rheumatoid arthritis and in other autoimmune diseases.

This work was supported by the Medical Research Council (MRC), Gilman Foundation, Kay Kendall Trust, and Wellcome Trust. We thank Dr J. Phillips and the staff of the Therapeutic Antibody Centre for antibody manufacture; Ms Mary Smith for metrology and thermography; Ms Helen Waller, Mr Peppe Rebello, and Ms Sally Coles for expert technical assistance; Dr A. Crisp and Dr A. Nichols for referring patients for this study; and the staff of Ward F5 at Addenbrooke’s Hospital. J. D. I. is an MRC clinician scientist and a research fellow of Downing College, Cambridge. CAMPATH is a trademark owned by Wellcome Foundation, Beckenham, Kent.

REFERENCES

Maternal relaxin concentrations in diabetic pregnancy

B. G. STEINETZ P. G. WHITAKER J. R. G. EDWARDS

Maternal serum concentrations of relaxin, an insulin homologue produced both by the corpus luteum of pregnancy and by the fetoplacental unit, are highest in the first trimester and fall to their lowest level in the third trimester. Relaxin is thought to influence carbohydrate metabolism in the uterus, and it has been suggested that serum concentrations of relaxin in diabetic women are higher than those of non-diabetic women.

We show that maternal serum relaxin concentrations are significantly higher at each stage of pregnancy in insulin-dependent diabetic mothers than in non-diabetic mothers. This elevation in relaxin concentrations is not related to other indices of diabetic control. The physiological importance of the higher concentrations of relaxin in the serum of diabetic women—in particular, whether they contribute to the higher incidence of major anomalies in the fetuses of diabetic mothers—is yet to be determined.