Changes in immune function in patients with rheumatoid arthritis following treatment with sodium aurothiomalate

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SUMMARY The mitogenic response of peripheral blood lymphocytes from 21 patients with rheumatoid arthritis to concanavalin-A (con-A), phytohaemagglutinin (PHA), and pokeweed mitogen (PWM) was significantly lower than in 30 normal subjects. After 15–24 weeks' treatment with sodium aurothiomalate (GST) the response to these mitogens rose to within the normal range. Improvement over pretreatment values was significant for con-A and PWM measured as area under the dose response curve but only for con-A if response at optimal mitogen concentration is the sole criterion. The improvement in PHA response was not significant with either method of measurement. There was an improvement in disease activity by 15–24 weeks as measured by a fall in serum C-reactive protein (CRP), IgM rheumatoid factor (RF), C1q binding activity (C1qBA), and Ritchie articular index. Con-A lymphocyte responsiveness was inversely related to serum CRP levels, but measurements of disease activity were otherwise unrelated to lymphocyte mitogen responsiveness. The observed improvement in peripheral blood lymphocyte responsiveness during gold treatment contrasts with the suppressive effect of gold in vitro. We suggest that the improvement in lymphocyte function is due to the lessening of rheumatoid disease activity during gold treatment, and that the low serum gold levels in our patients were insufficient to mask this effect. Sera from some of our patients were capable of suppressing the function of normal lymphocytes, and this was less apparent after treatment. The suppressive effect of sera correlated with C1qBA. Suppressive factors in serum, including possibly immune complexes, may be one factor leading to suppression of lymphocyte function during rheumatoid arthritis. Such an inverse relationship between humoral and cellular immune mechanisms might influence the clinical expression of rheumatoid arthritis.

Gold salts have been shown in controlled trials to be effective in the treatment of rheumatoid arthritis.1–3 However, the means by which gold inhibits inflammation in rheumatoid arthritis is unknown, although a wide variety of mechanisms have been investigated.4 As immunological processes, and especially the function of lymphocytes,5 are thought to be important in the pathogenesis of the disease, the effects of gold on immune mechanisms have been studied. A number of studies6–10 have shown that gold present at the initiation of lymphocyte cultures in vitro suppresses lymphocyte responsiveness to stimulation by mitogens and antigens. This effect is most apparent with gold concentrations of 10–100 μg/ml and has been shown to be due to an effect on monocytes. Rosenberg and Lipsky11 have also shown that gold can inhibit pokeweed mitogen induced immunoglobulin production by human lymphocytes. Gold has an inhibitory effect on the mixed leucocyte reaction7 9 10 12 and cell-mediated cytotoxicity9 12 13 when present at the initiation of culture.9 13 Thus, there is evidence from in-vitro experiments with human peripheral blood mononuclear cells that gold inhibits several lymphocyte functions, possibly due to its effect on monocytes. Other effects on macrophages and monocytes include diminution in pinocytosis14 and phagocytosis14 15 in peripheral blood monocytes and diminution of phagocytosis in synovial macrophages.16

Accepted for publication 2 July 1980
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The study of the effect of in-vivo administration of gold on antibody responses in animals has given results which conflict with the in-vitro results with human lymphocytes, which suggest an overall suppressive effect on lymphocyte responses. Measle showed an increased antibody response to sheep red blood cells and type III pneumococcal polysaccharide when gold was injected at the same time as the antigen. Scheiffarth et al. showed a similar effect in mice when gold was given at the same time as antigen but a decrease in antibody response when gold was given 12 weeks prior to the antigen. Persellin et al. found that gold did not inhibit antibody response to typhoid and paratyphoid vaccine or bovine serum albumin in rabbits. Walz et al. found that sodium aurothiomalate (GST), in contrast to triethylphosphine gold (Auranofin), increased antibody response to sheep red blood cells and fibroblasts in mice. In a similar manner T cell mediated immunity did not seem to be affected by gold salts, in that GST administration did not affect the skin response of guinea-pigs to dinitrochlorobenzene or diphthera toxoid. One of the few positive effects of gold observed in animals is the suppression of the phagocytic capacity of macrophages and polymorphs.

In spite of the apparent lack of effect of gold on most normal immunological mechanisms tested in vivo in animals, in-vivo studies in patients with rheumatoid arthritis have shown some changes in immunological parameters. Gottlieb et al. and Lorber et al. have shown falls in serum immunoglobulin levels and rheumatoid factor during gold treatment of rheumatoid arthritis. There is a fall in CRP and other acute-phase reactants during gold treatment and a fall in the phagocytic capacity of macrophages as measured by a skin window technique. A small number of groups have studied the effect of gold administration on the peripheral blood lymphocyte function of patients with rheumatoid arthritis. These results have been conflicting, with one group suggesting a diminution in lymphocyte responsiveness consistent with an 'immuno-suppressive' role for gold. One study with only 8 patients showed no significant difference of lymphocyte mitogen responsiveness in gold-treated patients compared with 5 normal persons, and another showed an improvement in lymphocyte responsiveness.

We decided to study the responsiveness of peripheral blood lymphocytes to the mitogens Concanavalin–A (Con–A), phytohaemagglutinin (PHA), and pokeweed mitogen (PWM) in patients before gold therapy and during treatment, together with concurrent measurements of serum C-reactive protein (CRP), C1q binding activity (C1qBA), rheumatoid factor (RF) latex titre, and clinical measurement of disease activity. We hoped to determine whether gold treatment given in vivo suppressed lymphocyte responsiveness as suggested by the in-vitro data and whether any change in lymphocyte responsiveness could be related to serum and clinical indicators of disease activity or to serum gold levels.

Materials and methods

Twenty-one patients with definite or classical rheumatoid arthritis of whom 17 were females and 4 males, mean age 57.9 ± 9.6 years (mean ± SD) with a mean disease duration of 7.8 ± 10.9 years were studied; 16 were seropositive and 5 persistently seronegative. All patients continued to take nonsteroidal anti-inflammatory drugs during the study.

GOLD DOSAGE AND PATIENT ASSESSMENT

Patients were treated with 2 different gold dosage schedules: one high dose and one low dose. The high dose schedule was 50 mg GST weekly to a total dose of 1 g and then 50 mg monthly. The low dose schedule was 10 mg GST weekly to a total of 200 mg and then 20 mg monthly. Ten patients commenced the low dose schedule and 11 the high dose schedule. At monthly intervals the same observer recorded morning stiffness, grip strength, Ritchie articular index, and total proximal interphalangeal (PIP) joint circumference. Blood was taken at each visit for the measurement of CRP, C1qBA, and latex RF titre.

CONTROL SUBJECTS

Twenty-three inpatients being treated for back pain of noninflammatory origin and 7 healthy staff members formed the control group (18 females and 12 males, mean age 43.5 ± 13.7 years). The back pain patients were taking nonsteroidal anti-inflammatory drugs similar to those being taken by the rheumatoid subjects.

LYMPHOCYTE TRANSFORMATION

Blood anticoagulated with heparin (10 IU/ml) was collected for lymphocyte transformation studies at the commencement of gold therapy and at least once during treatment. Lymphocytes were separated on Trisil/Ficoll gradients and cultures carried out as previously described. Lymphocyte cultures were stimulated with Con–A (Miles-Yeda) at 1, 5, 10, and 20 μg/ml; PHA (Wellcome) at 0–01, 0–1, 1, and 10 μg/ml and PWM (Gibco) at 1/200, 1/800, 1/1600, and 1/3200 dilutions. Optimal mitogen concentrations established in preliminary experiments were...
con−A 10 μg/ml, PHA 1 μg/ml, and PWM 1/800 dilution. Cultures were pulse-labelled for the last 24 hours of incubation with 0·15 μCi tritiated thymidine (Radiopharmaceutical Centre, Amersham), specific activity 0·15 Ci/mM. Con−A and PHA cultures were incubated for 72 hours and PWM for 96 hours and results determined by the incorporation of tritiated thymidine.

**Cultures in Patients’ Serum**

Cultures were carried out to determine the effect of patients’ serum before and after GST treatment on the mitogen responsiveness of normal lymphocytes. Test serum at 20% concentration was incubated with 2 × 10⁶ normal lymphocytes for 2 hours in a total volume of 100 μl of tissue culture medium. Con−A was then added in 100 μl of tissue culture medium to give a final optimal concentration of 10 μg/ml and a final serum concentration of 10%. Subsequent culture was as previously described except that 0·5 μCi of tritiated thymidine, specific activity 0·5 Ci/m, was added during the last 24 hours of culture. Cultures were carried out in quadruplicate and results expressed as disintegrations per minute (DPM) with patients’ serum/DPM in pooled normal serum. Two such experiments were carried out on paired sera from 14 of these patients.

**C-Reactive Protein**

CRP levels were measured by single radial immunodiffusion in 1% agar in phosphate buffered saline, pH 7·2, containing 0·1% rabbit anti-CRP (Behringwerke).

**Rheumatoid Factor**

IgM rheumatoid factor levels were estimated by latex agglutination in tubes. All sera relating to each patient were estimated in the same batch to avoid within-patient variation. Appropriate positive and negative control sera were included in each batch of tests. Sera for CRP and RF measurements were stored at −20°C.

**Clq Subcomponent**

The Clq subcomponent of complement was isolated from human serum by the method of Reid et al. and radioiodinated by a modification of the chloramine T method. Specific radioactivity ranged between 0·4 and 0·8 μCi/μg Clq.

**125I Clq Binding Assay**

The modified 125I Clq binding test was performed as described by Zubler et al. Sera for estimation of ClqBA were stored at −70°C. All sera relating to an individual patient were tested in a single batch.

**Serum Gold Levels**

Blood was taken for measurement of serum gold levels weekly for the first 6 weeks of therapy then at 2 months, 4 months, and 8 months of treatment. Specimens were taken prior to the next gold dose. Levels were measured on a Perkin-Elmer Model 303 Atomic Absorption spectrophotometer.

**Evaluation of Results**

Lymphocyte transformation results are expressed either as DPM, log₁₀ DPM, or as area under the dose response curve. As lymphocyte transformations were carried out at different time intervals during therapy, results were grouped into periods of 10 weeks centred on 0, 10, and 20 weeks. Results presented here are those prior to the commencement of gold therapy and after 15–24 weeks of treatment, the 10-week period centred on 20 weeks when patients changed from weekly injections to maintenance therapy.

Of the 21 patients studied 1 has no results for con−A stimulation and another no results for PHA and PWM, because of technical failures. Hence results for 20 patients are shown for each mitogen. Of the 30 controls 2 had repeat determinations of mitogens responsiveness, and so up to 32 results are shown. Fewer controls were tested with PWM, hence 25 results. The numbers of results are smaller both for patients and for controls when expressed as area under the dose response curve, as results were not available at all mitogen concentrations in some cases. Hence area under the curve results could be calculated for 15 patients with con−A (26 controls) 14 for PHA (29 controls), and 14 for PWM (20 controls).

**Statistical Analysis**

For statistical analysis, where lymphocyte transformation results are shown as DPM or area, non-parametric statistics have been used. Lymphocyte responses for patients at zero and 15–24 weeks are compared by Wilcoxon’s matched-pairs signed-ranks test. This test was also used to compare CRP, latex titre, Clq binding activity, and Ritchie articular index results concurrent with the lymphocyte transformation data. Lymphocyte responsiveness of patients and normal persons was compared by the Mann-Whitney U test. Where lymphocyte responses are shown as log₁₀ DPM, comparison has been made using Student’s 𝑡 test, as log transformation has been assumed to have ‘normalised’ the results. Two-tailed tests were used throughout.

**Results**

**Clinical Response to Gold Therapy**

A successful outcome of therapy was arbitrarily
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defined as a 50\% or greater fall in CRP or erythrocyte sedimentation rate (ESR) together with 3 out of 4 of the following improvements in clinical measurements: 50\% fall in early morning stiffness, 50\% improvement in the Ritchie articular index, 25\% increase in the grip strength, and a 15 mm fall in total PIP joint circumference. When a measurement was normal at the start of the study, it was ignored for the purposes of calculation of outcome of therapy, and an improvement in 2 out of 3 of the remaining measurements was accepted as evidence of improvement. By this definition 16 patients responded to therapy and 5 did not; 3 patients on the high dose regimen and 2 on the low dose regimen. This difference has not been made to compare results according to gold dosage schedule, especially as some patients were changed from one regimen to another.

**SERUM GOLD LEVELS**

The mean highest serum gold level for the 21 patients was 2.39 ± 1.7 μg/ml (± SD). The mean for the 10 patients on low dose therapy was 0.96 ± 0.3 μg/ml and for the 11 patients on high dose therapy 2.37 ± 1.2 μg/ml. The highest serum gold level seen in any patient was 5.1 μg/ml.

**LYMPHOCYTE TRANSFORMATION**

Before the start of treatment lymphocytes from patients with rheumatoid arthritis had significantly depressed responsiveness at optimal concentrations of all 3 mitogens tested (Fig. 1). After treatment the difference from normal persons remained significant with PWM. However, when only these optimal concentrations are considered, the improvement in lymphocyte responsiveness over pretreatment levels after 15–24 weeks of gold treatment is significant only with con–A.

As shown in Fig. 2, comparing lymphocyte responsiveness only at optimal concentrations ignores differences at other mitogen concentrations. To take account of these differences, results can be expressed as area under the dose response curve. When expressed in this way (Fig. 3), pretreatment lymphocyte responsiveness to PWM, PHA, and con–A was significantly depressed when compared to normals. After 15–24 weeks of therapy with GST there was a significant improvement in lymphocyte responsiveness to con–A and PWM but not to PHA. The improvement after 15–24 weeks of gold therapy was such that lymphocyte responsiveness is not significantly different from normal for any of the mitogens tested.

![](image.png)

Fig. 1 Improvement in lymphocyte response at optimal mitogen concentration in patients with rheumatoid arthritis after 15–24 weeks of gold treatment. Lymphocyte responses are shown at optimal mitogen concentrations: con–A 10μg/ml, PHA 1 μg/ml, PWM 1/800 dilution. Results are expressed as log₁₀ disintegrations per minute. NL indicates values for normal persons; 0 and 15–24 values for patients with rheumatoid arthritis before and after 15–24 weeks of gold therapy respectively. Bars represent mean ± 1 standard deviation. Initial values are significantly different from normal persons for con–A (P<0.01), PHA (P<0.05), and PWM (P<0.01) by Student’s t test. The improvement in values between 0 and 15–24 weeks is significant only for con–A (P<0.01) by paired Student’s t test. After treatment values at 15–24 weeks are significantly below normal only for PWM (P<0.01) by Student’s t test.
Fig. 2 Mean lymphocyte response to stimulation with concanavalin-A in patients with rheumatoid arthritis at initiation of gold therapy and after 15–24 weeks of treatment, in comparison with normal persons. Open circles represent mean lymphocyte response for 15 patients with rheumatoid arthritis before therapy, closed circles values for the same patients after 15–24 weeks of gold therapy, triangles values for 26 normal persons. These are the same patients and normal persons for whom results are shown as area in Fig. 3. Flags represent 1 standard error of the mean. There are significant differences between values before and after gold therapy by Wilcoxon’s matched-pairs signed-rank test at con-A concentrations of 1 μg/ml (P = 0·01), 5 μg/ml (P < 0·01), and 10 μg/ml (P < 0·01). There is no significant difference at 20 μg/ml. Values for normal persons are significantly different from pretreatment values for patients with rheumatoid arthritis at all mitogen concentration: con-A 1 μg/ml (P < 0·01), con-A 5, 10, and 20 μg/ml (P < 0·001) by Mann-Whitney U test. Values for normal persons are not significantly different from those for rheumatoid subjects after gold therapy except at a con-A concentration of 20 μg/ml (P < 0·05).

Fig. 3 Improvement in lymphocyte mitogen response measured as area under the dose response curve in patients with rheumatoid arthritis after 15–24 weeks of gold treatment. Mean lymphocyte responses are shown in arbitrary units of area which are different for each mitogen. NL indicates values for normal persons, 0 and 15–24 values for patients with rheumatoid arthritis before and after 15–24 weeks of gold therapy respectively. Flags represent 1 standard error of the mean. The difference between values at 0 and 15–24 weeks is significant for con-A (P < 0·001) and PWM (P < 0·02) but not for PHA by Wilcoxon’s matched-pairs signed-ranks test. Pre-treatment levels are significantly different from normal persons for con-A (P < 0·001) and PWM (P < 0·001) and PHA (P < 0·05) by Mann-Whitney U test. There is no significant difference between normal values and those for patients with rheumatoid arthritis at 15–24 weeks.
mitogen responsiveness there was no correlation between mitogen responsiveness and ClqBA, RF latex titre, or Ritchie index. There was a weak inverse correlation between lymphocyte responsiveness to con–A, as measured by area under the dose response curve, and serum CRP concentration ($r = -0.4$, $P = 0.02$).

EFFECT OF PATIENTS’ SERUM ON NORMALLY RESPONSIVE LYMPHOCYTES

Paired sera from 14 patients before and after 15–24 weeks of gold treatment were tested for their effect on the response of normal lymphocytes to an optimal concentration of con–A. In all 14 cases pre-treatment sera supported lymphocyte transformation less well than the corresponding sera after treatment. Before treatment 8 sera were suppressive compared to pooled normal serum, whereas after treatment only 2 sera were suppressive (Fig. 4). The difference between pre- and post-treatment values is significant ($P<0.001$) by paired Student’s $t$ test. In order to assess whether this effect was related to serum factors associated with disease activity a correlation was sought between the effect of patients’ sera on normal lymphocyte responses and CRP, RF latex titre, and ClqBA. There was no correlation with CRP and RF latex titre, but there was a significant inverse relationship between the responsiveness of normal lymphocytes preincubated in patients’ serum and ClqBA ($r = 0.63$, $P<0.001$).

Discussion

In our group of 21 patients with rheumatoid arthritis lymphocyte responsiveness to the mitogens con–A, PHA, and PWM was significantly lower than that of a normal control group. This is consistent with most previous observations except for the PWM response, which is generally considered to be normal. After 15–24 weeks of gold therapy lymphocyte responsiveness measured as area under the dose response curve returned to normal levels with all 3 mitogens. The improvement over pretreatment values was significant for con–A and PWM when measured as area and for con–A when response at optimal concentration is considered. Thus, in this

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Table 1  Improvement in C-reactive protein, latex titre, Clq binding activity and Ritchie articular index with gold therapy. Values shown represent mean ± standard error of the mean for 21 patients with rheumatoid arthritis treated with sodium aurothiomalate and who had lymphocyte responsiveness measured at the beginning of therapy and after 15–24 weeks of treatment. Differences are significant for all measurements by Wilcoxon’s matched-pairs signed-ranks test: CRP, $P<0.001$; Clq binding activity, $P<0.01$; Ritchie articular index, $P<0.001$. There is a significant fall in latex titre for the 16 seropositive patients ($P<0.001$), though this mean fall, when expressed as number of tube dilutions, represents a drop of only 1 tube.

<table>
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<th>Weeks of gold therapy</th>
<th>C-reactive protein</th>
<th>Latex titre</th>
<th>Clq binding activity</th>
<th>Ritchie articular index</th>
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</thead>
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<td>7750±2750</td>
<td>34.1±4.3</td>
<td>9.6±1.7</td>
</tr>
<tr>
<td>15–24</td>
<td>12.5±3.5</td>
<td>3800±1400</td>
<td>26.2±3.4</td>
<td>2.5±0.8</td>
</tr>
</tbody>
</table>

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Fig. 4  The effect of sera from 14 patients with rheumatoid arthritis before and after 15–24 weeks of gold therapy on the response of normal lymphocytes to concanavalin–A. Normal peripheral blood lymphocytes were preincubated for 2 hours with 20% test serum before addition of an optimal concentration of con–A (10 µg/ml). This figure shows the results of 2 such experiments. Results are expressed as DPM in rheumatoid serum/DPM in pooled normal serum. All sera collected before treatment supported lymphocyte transformation less well than the corresponding sera after treatment. This difference is significant ($P<0.001$) by paired Student’s $t$ test. Compared to pooled normal serum 8 sera were suppressive prior to therapy but only 2 remained suppressive after therapy.
group of patients there was an overall trend towards improvement of lymphocyte mitogen responsiveness during gold treatment. This contrasts with the suppressive effects of gold salts added to lymphocyte cultures in vitro.

There are only a small number of limited studies on lymphocyte responsiveness in patients with rheumatoid arthritis treated with gold. Percy et al. found an improvement in lymphocyte responsiveness to PHA in patients treated with GST. Their results are not comparable to ours, as they measured lymphocyte responsiveness as normal or abnormal according to whether lymphocyte transformation index (LTI) was greater or less than 10. Comparing the normal or abnormal LTI with active or inactive disease, they found an association between subnormal LTI and active disease. Beyond this they do not show a comparison of pretreatment and post-treatment lymphocyte responsiveness in that paper. A previous paper in which this was shown included patients treated with D-penicillamine and so cannot be compared with our results. Strong et al. were unable to show a significant difference in lymphocyte responsiveness to PHA and PWM between 5 normal persons and 8 patients with rheumatoid arthritis. They did not compare pre- and post-gold treatment results, and the numbers in their study are very small. Lorber et al. suggested that gold treatment leads to suppression of lymphocyte responsiveness to PHA. They give data as percentage change in LTI from pretreatment levels. Five of their 15 patients, who were treated for less than 10 weeks, in fact show an increase in LTI. No indication is given as to whether responsiveness was significantly different from pretreatment levels in these 15 patients.

In our patients there was an improvement in disease by 15–24 weeks of GST treatment. This was reflected by significant falls in CRP, C1qBA, IgM rheumatoid factor, and Ritchie articular index. The falls in RF titre and CRP are consistent with the findings of others. The only significant relationship between these measurements of disease activity and lymphocyte responsiveness was an inverse relationship between lymphocyte responsiveness to con–A measured as area and serum CRP. Percy et al., using their arbitrary normal/abnormal classification of lymphocyte transformation, showed an association between improvement in disease and improvement in lymphocyte response. In a similar manner on our arbitrary definition of a response to gold therapy there is a significant association between a normal con–A concentration at 15–24 weeks and a favourable response to gold therapy ($\chi^2 = 10.4$, $P = 0.01$ with Yates's correction for small numbers). However, the numbers are small (4 out of 5 nonresponders outside the normal range after treatment) and the association did not hold for PHA and PWM. Thus, our results give limited evidence for a relationship between objective measurements of disease activity and lymphocyte responsiveness, in spite of the fact that an overall improvement in lymphocyte function occurred concurrently with improvement in these measurements of disease activity.

The overall trend towards improvement in peripheral blood lymphocyte responsiveness that we have observed contrasts with the suppressive effect of gold salts added to lymphocyte cultures in vitro, as discussed previously. We think that a possible explanation of this apparent contradiction might be as follows. Gold, which reaches high levels in synovial membrane, might have a local effect on the rheumatoid inflammatory process, possibly owing to its suppressive action on lymphocyte function. Owing to this amelioration of disease activity there might be a fall in the production of factors released into the circulation, which could have a suppressive effect on lymphocytes. A fall in the level of these suppressive factors, due to an improvement in disease activity, would lead to an improvement in peripheral blood lymphocyte responsiveness. This improvement would be opposed by gold present in serum, but at the low levels of serum gold in our patients the net result would be an improvement in lymphocyte responsiveness. Lorber et al.'s observation of suppression of lymphocyte responsiveness in gold treated patients might be due to the fact that their patients were treated so as to keep their serum gold levels prior to their next injection above 3 µg/ml. This group has previously shown that the high levels of serum gold immediately after injection are associated with a depression of lymphocyte response to con–A and PHA when compared to levels before injection.

An important aspect of the above hypothesis is the production of factors capable of suppressing lymphocyte function during the rheumatoid inflammatory process. We have presented evidence that sera from our patients suppressed the function of normal lymphocytes and that after gold treatment their sera were less suppressive. The fact that this suppression correlated with C1qBA suggests that it was related to disease and not due to changes in drug concentration present in the patients' sera. This lends some support to the above hypothesis, though it seems unlikely that a suppressive effect from C1q binding material (immune complexes) could fully explain the lymphocyte function changes we observed during gold treatment, as these changes did not correlate with C1qBA.

If immune complexes do play a role in suppressing
lymphocyte function in patients with rheumatoid arthritis, as suggested by our data, this would provide a link between humoral and cell-mediated immune functions in rheumatoid arthritis. Inversely related changes in humoral and cell-mediated immune responses might underlie some of the changes in character that occur during the course of a patient’s rheumatoid disease. In view of this we are currently further investigating the nature of the suppressive effect of these sera.

During this study John Highton was supported initially by a grant from Eli Lilly and Co. Ltd. and subsequently by an Arthritis and Rheumatism Council Fellowship. We thank Dr R. Grahame for allowing his patients to be studied, Ms L. Griffiths for help in the clinical assessment of patients, Dr Andrew Taylor, University of Guildford, for the measurement of serum gold levels, and Ms P. Burke for technical assistance in the estimations of C1q binding activity.

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doi: 10.1136/ard.40.3.254

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