Inhibition of Interleukin-2–Induced Tumor Necrosis Factor Release by Dexamethasone: Prevention of an Acquired Neutrophil Chemotaxis Defect and Differential Suppression of Interleukin-2–Associated Side Effects

By James W. Mier, Gloria Vachino, Mark S. Klempner, Frederick R. Aronson, Richard Noring, Steve Smith, Eugene P. Brandon, Wally Laird, and Michael B. Atkins

High concentrations of tumor necrosis factor (TNF) alpha have been detected in the plasma of patients undergoing immunotherapy with interleukin 2 (IL-2), suggesting that this cytokine may play a role in the fever and shock-like state induced by the administration of high-dose IL-2. Dexamethasone has been shown to inhibit the synthesis of TNF by monocytes activated in vitro by endotoxin. To determine if dexamethasone can exert a similar suppressive effect on IL-2–induced TNF synthesis in vivo, the concentration of TNF alpha was measured in plasma samples serially obtained (a) from cancer patients participating in a phase I dose escalation clinical trial with high-dose IL-2 administered in conjunction with dexamethasone (IL-2/Dex) and (b) from patients participating in concurrent studies with IL-2 alone. In contrast to the high plasma levels of TNF alpha detected in patients receiving IL-2 alone, TNF levels in most of the IL-2/Dex patients remained below the threshold of detectability of our TNF radioimmunoassay. The concurrent administration of dexamethasone also prevented the IL-2–induced increase in serum levels of C-reactive protein, a hepatic acute phase reactant whose synthesis is regulated by proinflammatory cytokines such as TNF. The steroid-treated patients also failed to develop the neutrophil chemotactic defect characteristic of IL-2 recipients. The concomitant administration of dexamethasone increased the maximum tolerated dose of IL-2 approximately threefold and markedly reduced the hypotension and organ dysfunction ordinarily observed in these patients. These results demonstrate that dexamethasone inhibits the release of TNF into the circulation of patients undergoing immunotherapy with IL-2. They further suggest that the altered spectrum and reduced severity of IL-2 side effects observed in patients receiving dexamethasone may be attributable in part to the suppressive effect of steroids on IL-2–induced TNF synthesis.

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dose (MTD) for IL-2 was increased by the inclusion of dexamethasone in the regimen was not determined. Likewise, the effects of steroids on plasma TNF levels and on other parameters influenced by IL-2-inducible proinflammatory cytokines were not addressed. This phase I study with IL-2 and dexamethasone was therefore conducted to determine the MTD, to further define the toxicity profile and its biological basis, and to assess the antineoplastic potential of IL-2 administered with steroids.

MATERIALS AND METHODS

Study design. The 19 patients participating in the trial with high-dose IL-2 administered in conjunction with dexamethasone (IL-2/Dex) were adults with advanced carcinoma either refractory to standard therapy or for which no conventional treatment was available. All patients had measurable or evaluable disease and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. Patients selected for treatment with IL-2/Dex were ineligible for other IL-2 protocols. This study was approved by the Human Investigation Review Board at the New England Medical Center and written informed consent was obtained from each patient. Patients were evaluated for participation in this investigation in the New England Medical Center Oncology Clinic and treatment was administered in the Clinical Study Unit at the New England Medical Center.

No patient participating in this study received concomitant chemotherapy or radiation therapy. Patients received 4 mg oral dexamethasone every 6 hours beginning 24 hours before initiating IL-2 treatment and continuing for 24 hours after completing treatment. The recombinant IL-2 (Proleukin) used in these studies was provided by Cetus (Emeryville, CA) and all doses are expressed in International Units (IU) (1.0 mg of Proleukin = 1.8 × 10^7 IU). IL-2 was administered in bolus intravenous injections every 8 hours for 14 doses per treatment course. Courses were repeated at 2-week intervals. The first four patients were treated at 1.5 × 10^6 IU/kg, after which the dose was escalated in accordance with the protocol, ultimately to 2.4 × 10^6 IU/kg. The highest dose tolerated by at least three patients was designated the MTD. Patients were evaluated for tumor response after each course and those with progressive disease were removed from the study. Those showing tumor regression after four courses of IL-2 were continued on treatment. In addition to IL-2/Dex, all patients received oral acetaminophen and ibuprofen to minimize IL-2-induced fever and rhabdomyolysis to reduce the risk of gastritis and peptic ulceration. Meperidine was administered as needed for chills, diphenhydramine for pruritis, Lomotil (Searle, Skokie, IL) and Imodium (Janssen, Piscataway, NY) for diarrhea, and prochlorperazine and perphenazine for nausea and vomiting.

For the purpose of comparison, blood samples were also obtained from patients participating in an National Cancer Institute (NCI)-sponsored protocol with high-dose IL-2 (6.0 × 10^6 IU/kg every 8 hours × 14 doses) without dexamethasone. This study was conducted concurrently with the IL-2/Dex clinical trial.

Assay for TNF alpha. Plasma samples were obtained before and 2, 4, and 8 hours after the first IL-2 injection. TNF alpha levels were determined by radioimmunoassay (RIA) as previously described. C-reactive protein assay. Serum samples were obtained before the first IL-2 injection and 24 and 48 hours later. C-reactive protein (CRP) levels were measured by enzyme-linked immunoabsorbent assay as described.

Neutrophil chemotaxis assays. Blood samples for neutrophil function studies were obtained before the first IL-2 injection and at the end of the first course of IL-2 (day 4 or 5). Chemotaxis assays were also performed on neutrophils isolated from the blood of normal volunteers drawn on the same day as the patient samples. Leukocytes containing 95% to 98% PMN were isolated by Ficoll/Hypaque density gradient centrifugation and dextran sedimentation as described. Residual erythrocytes were lysed with hypotonic saline and the neutrophils were suspended in Hanks' balanced salt solution. The chemotaxis assays were carried out as previously described using 10^-4 mol/L f-met-leu-phe (fMLP) as the chemotactic stimulus. The chemotactic index was determined by calculating the percent stimulated migration above random (unstimulated) migration. Student's t test was used for statistical evaluation of the findings.

Surface phenotype analysis. Heparinized venous blood samples were obtained immediately before and 4 hours after the first IL-2 injection and the PBMCs were isolated by density gradient centrifugation with Ficoll/Hypaque. The surface phenotype of the PBMCs was determined with a FACS Analyzer (Becton Dickinson, Sunnyvale, CA) using a panel of monoclonal antibodies, including OKT3 (Ortho Diagnostics, Raritan, NJ); Leu 11b, Leu 16, and Leu M3 (Becton Dickinson); and fluorescein-conjugated, affinity-purified rabbit antimouse Ig (ab)2 (Cappel Laboratories, West Chester, PA).

RESULTS

Suppression of IL-2-induced TNF alpha production by dexamethasone. In order to facilitate a direct comparison between our phase I dose escalation IL-2/Dex regimen and the NCI-sponsored high-dose IL-2 alone protocol, the serial plasma samples used in the TNF assays shown in Fig 1 were obtained from those IL-2/Dex patients treated with the same IL-2 dose as that received by those patients participating in the NCI clinical trial (6.0 × 10^6 IU/kg) (Fig 1A and B) or with IL-2/Dex at the MTD (1.8 × 10^6 IU/kg) (Fig 1C). The
6.0 \times 10^5 \text{ IU/kg} dose used in the NCI regimen represents the MTD for IL-2 administered without steroids. As previously mentioned, the samples used in these assays were all obtained after the first IL-2 injection regardless of the specific IL-2 regimen. As shown in Fig 1A, a single injection of IL-2 elicited a marked increase in the plasma level of TNF alpha in all six patients treated with IL-2 alone. Peak levels in excess of 1,000 pg/mL were occasionally detected in these patients 2 hours after the IL-2 injection. Conversely, only one of five patients receiving a similar dose of IL-2 while taking dexamethasone had a comparable increase in the plasma TNF alpha level. This particular patient was notable in that he became severely hypotensive after the IL-2 injection. In accordance with the IL-2/Dex protocol, treatment was interrupted and the patient was subsequently retreated with a 50% IL-2 dose reduction. He again became hypotensive, necessitating his removal from the study. Serial plasma samples were also obtained in four additional patients treated with IL-2/Dex at the MTD (1.8 \times 10^6 \text{ IU/kg}) and none had an increase in their plasma TNF alpha levels.

Effects of IL-2/Dex on serum CRP levels. We previously demonstrated that IL-2 administration increased the serum level of the hepatic acute phase reactant CRP.\textsuperscript{2} This effect was attributed to the release of secondary cytokines including IL-1 and TNF,\textsuperscript{17} which directly stimulate hepatic acute phase protein synthesis.\textsuperscript{3,34} Consistent with the changes in plasma TNF levels, serum CRP levels increased in five of the six patients treated with IL-2 alone (Fig 2). The only IL-2/Dex patient whose CRP level rose after beginning treatment was the one whose TNF alpha level increased after IL-2 administration. This patient had an abnormal pretreatment CRP level that rapidly declined after terminating IL-2 therapy and initiating antibiotic treatment for a urinary tract infection. CRP levels from the four patients treated with IL-2 at the MTD with dexamethasone remained within the normal range.

Effects of IL-2/Dex on leukocyte differential counts and PBMC phenotype. The administration of IL-2 promptly alters the differential leukocyte count, inducing the release of immature granulocytes and the disappearance of lymphocytes from the circulation.\textsuperscript{3} To determine if the concomitant administration of steroids would influence these IL-2-induced changes in the leukocyte differential counts, the total leukocyte count and differential were determined before and 4 hours after a single injection of either IL-2 alone or IL-2/Dex at the MTD. As expected, and as shown in Table 1, all but one of the patients who had received dexamethasone for 24 hours had a higher WBC count before receiving IL-2 than those not receiving steroids. Moreover, a greater percentage of the leukocytes in the steroid-treated patients were neutrophils. In both treatment groups, the injection of IL-2 induced the release of bands and reduction in the number of circulating lymphocytes.

In addition to the differential leukocyte counts, the PBMC surface phenotype was also determined. PBMCs were obtained before and 4 hours after the first IL-2 injection from five patients treated with IL-2 alone and from a matching group of IL-2/Dex patients. The cells were subjected to cytofluorographic analysis with several monoclonal antibodies. In addition to the precipitous decline in the total number of circulating lymphocytes, the percent of those expressing CD3 fell rapidly after the IL-2 administration. This effect was especially pronounced in patients concurrently receiving dexamethasone. As shown in Fig 3, the percentage of PBMC expressing CD3 declined from 18% \pm 11% to 10% \pm 7% (mean decline of 52%) in the IL-2 alone treatment group and from 13% \pm 6% to 2% \pm 3% (mean decline of 84%) in the IL-2/Dex group. No consistent change in the percentage of PBMCs expressing CD16 (a marker for

### Table 1. Effects of Treatment on Circulating Leukocytes

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<th>Patient</th>
<th>Time (h)</th>
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<td>4</td>
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<td>0</td>
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<td>66</td>
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<td>28</td>
<td>0</td>
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natural killer (NK) cells) or Leu M3 (a monocyte surface antigen) was observed 4 hours after an IL-2 injection regardless of whether the patient was receiving steroids. Consistent with previous reports on the suppressive effects of steroids on NK activity, PBMC cytolytic activity against K562 cells was essentially undetectable in patients receiving dexamethasone both before and after IL-2 administration (data not shown).

Effects of IL-2/Dex on neutrophil chemotaxis. We recently described a transient but profound defect in neutrophil chemotaxis in patients undergoing treatment with IL-2 and postulated that this abnormality contributed to the 15% to 35% incidence of staphylococcal aureus bacteremia in these patients. Because a similar defect can be induced in vitro by exposing normal neutrophils to TNF alpha and because dexamethasone suppresses the release of this cytokine in IL-2 recipients, we compared the chemotactic responses of the neutrophils of IL-2/Dex patients treated at the MTD (1.8 x 10^6 IU/kg) with the results of similar assays using neutrophils from patients receiving IL-2 alone. Before initiating treatment, the mean random (unstimulated) migration of neutrophils from patients in the IL-2 alone group was 62 ± 16 μm (range 40 to 83 μm) and that of the IL-2/Dex group was 68 ± 26 μm (range 25 to 98 μm), both of which were comparable with the results of same-day assays with normal donor neutrophils (mean 65 ± 15 μm, range 47 to 96 μm). After 4 to 5 days of treatment, random migration remained unchanged at 60 ± 17 μm (range 34 to 77 μm) for patients in the IL-2 alone group, 75 ± 17 μm (range 56 to 107 μm) for patients in the IL-2/Dex group, and 67 ± 18 μm (range 41 to 89 μm) for same-day controls. Although neutrophil random migration was unaffected by IL-2 treatment, fMLP-stimulated migration and the chemotactic index (the ratio of fMLP-stimulated to random migration) declined markedly in the IL-2 alone group from 73% ± 13% to 10% ± 27% (Fig 4). Indeed, in three of the five patients studied, the index fell below 0, indicating the complete abrogation of response to the fMLP. Conversely, the decline in the chemotactic index was minimal in all but one patient in the IL-2/Dex group. In these patients, the indices declined from 84% ± 52% to 55% ± 14%. In all but one of the five patients studied, the chemotactic index on day 5 was at least 68% of that before treatment, and in no instance did the index decline below 40%. Same-day normal control indices were 70% ± 14% on day 1 and 103% ± 66% on day 5.

Effects of dexamethasone on IL-2 toxicity. A total of 63 treatment cycles, 56 of which were at a dose of 6.0 x 10^6 IU/kg or higher, were administered in this trial. Consistent
with the suppressive effect of dexamethasone on the release of TNF, only 1 of the 19 patients participating in the IL-2/Dex study became hypotensive to the point of requiring pressor support. This patient developed rapid atrial fibrillation while receiving IL-2/Dex treatment at the MTD. None of the IL-2/Dex patients gained over 10% of their body weight as a consequence of IL-2-induced fluid retention. Only one patient developed a transient bilirubin elevation of greater than 2.5 and only two had reversible increases in serum creatinine of greater than 2.5 (both at IL-2 dose levels of $1.5 \times 10^6$ IU/kg or higher). Only one IL-2/Dex patient had an episode of bacteremia (staphylococcus epidermidis) and this arose as a complication of UGI endoscopy. No infections with staphylococcus aureus were detected in these patients. The most frequently encountered dose-limiting toxicities in the IL-2/Dex patients were diarrhea and cardiac arrhythmias. Severe diarrhea developed in 15 treatment courses, including 11 of the 34 in which the IL-2 dose was $1.5 \times 10^6$ IU/kg or higher. Atrial fibrillation developed in four patients. Only one patient developed significant disorientation during treatment. Patients usually recovered quickly from the side effects of the therapy and were discharged within 12 hours of their last dose of IL-2. Despite the reduction in the hypotension, capillary leak, and other side effects, tumor regression was still observed with this regimen. Of the 19 patients treated on the IL-2/Dex protocol, two patients (one each with renal cell and small bowel carcinoma) had a minimal response of approximately 3 months’ duration and a third patient (also with renal cell carcinoma) achieved a partial response lasting 6 months. All three responders were treated at the MTD (manuscript in preparation).20

**DISCUSSION**

The pathogenesis of the capillary leak syndrome and other IL-2 side effects is poorly understood. Several investigators have postulated that these phenomena are mediated at least in part through the release of IL-2-inducible secondary cytokines.1 Indeed, TNF alpha and beta,15,17 interferon gamma,16 IL-6,12 and to a lesser extent, IL-1 beta,15 are readily detectable in the plasma within hours of an IL-2 injection. Several of these intermediary cytokines induce fever, hypotension, and other side effects when administered to experimental animals or humans.18,19,21 For example, Horvath et al recently demonstrated that the administration of TNF to sheep induces respiratory distress and a marked augmentation of pulmonary lymphatic flow, findings consistent with an increase in the permeability of the pulmonary microcirculation.20 Fraker et al have shown that passive immunization of mice with anti-TNF antibodies increases the amount of IL-2 that can be safely administered.22 These results suggest that treatment modifications that reduce TNF generation are likely to reduce the toxicity of IL-2.

The concurrent administration of dexamethasone clearly ameliorates some aspects of IL-2 toxicity, thereby permitting the use of threefold higher doses of IL-2 ($1.8 \times 10^6$ IU/kg) than would otherwise be tolerated. In contrast to the severe toxicity experienced by patients receiving IL-2 without dexamethasone, our steroid-treated patients rarely developed the fever, dyspnea, confusion, renal insufficiency, and jaundice frequently observed in the absence of steroids. In fact, the dose-limiting toxicities of IL-2 in patients receiving steroids were for the most part gastrointestinal (diarrhea) and cardiac (supraventricular arrhythmias). Whereas the blood pressure of patients treated with dexamethasone and high doses of IL-2 ($>1.2 \times 10^6$ IU/kg) often decreased, the decline was gradual, mild, and readily reversible with intravenous fluids. Our steroid-treated patients generally did not develop appreciable edema and gained much less weight than patients treated with IL-2 alone. This finding differs from that reported by Vetto et al, who measured the same weight gain in their IL-2/LAK cell patients regardless of whether intravenous dexamethasone was included in the regimen.20 The basis for this difference is unclear but may be due to the difference in the routes of administration of the dexamethasone, the contribution of LAK cells, or earlier use of pressors by Vetto et al in the patients not treated with steroids.

Dexamethasone inhibits the lipopolysaccharide (LPS)-induced synthesis of TNF in vitro22 and appears to have a similar suppressive effect on IL-2-induced TNF synthesis in vivo (Fig 1). Although peak plasma TNF levels in excess of 1 ng/mL were detected in patients treated with IL-2 alone, only one of those receiving steroids had higher than background TNF levels. The fact that this particular patient became acutely hypotensive after his first IL-2 injection reinforces the view that TNF alpha may be responsible for the hemodynamic changes attributed to IL-2.10,11

Hepatic acute phase protein synthesis is regulated by pyrogenic cytokines such as IL-1, IL-6, and TNF.33-37 Normal hepatocytes and hepatocellular carcinoma cells synthesize several acute phase proteins in vitro when exposed to IL-1, TNF, and IL-2–activated PBMC supernatants, but not IL-2 itself.33 However, high levels of the acute phase reactant CRP are routinely detected in the serum after IL-2 administration.3 CRP has been shown to opsonize activated lymphocytes in vivo, resulting in complement activation at the cell surface, which may contribute to the capillary leak syndrome and ARDS associated with IL-2 therapy.39 Because glucocorticoids do not suppress TNF-induced acute phase protein synthesis in vitro,40 the failure of IL-2 administration to increase serum CRP levels in steroid-treated patients is most likely due to the suppression of secondary cytokine synthesis rather than direct inhibition of cytokine-induced hepatic acute phase protein synthesis.

We recently demonstrated that IL-2 administration results in a profound but reversible defect in neutrophil chemotaxis,5 which may be responsible for the high incidence of staphylococcus aureus bacteremia observed in patients undergoing IL-2 treatment.8 Other aspects of neutrophil function, including superoxide production, degranulation, and phagocytosis, remained normal or were enhanced during IL-2 treatment. The IL-2–associated abnormality in neutrophil chemotaxis can be simulated in vitro by exposing normal neutrophils to TNF26 and it is therefore likely that the modest decrement in neutrophil chemotaxis and the seemingly paradoxical reduction in the incidence of staphylococcal infection in patients receiving dexamethasone in addition to IL-2 are a consequence of the failure of IL-2 to induce the release of TNF in steroid-treated patients.
The endothelial-leukocyte adhesion molecule-1 (ELAM-1) is not expressed on unstimulated cultured endothelial cells but is readily inducible by adding TNF or IL-1 to the medium. Likewise, it is undetectable on endothelium in vivo except at sites of inflammation. Although IL-2 does not share with TNF and IL-1 the ability to induce ELAM-1 or to increase intercellular adhesion molecule-1 (ICAM-1) expression on cultured endothelial cells, these antigens are readily detected on the endothelial cells present in skin biopsy samples from patients undergoing treatment with IL-2, presumably a consequence of TNF release in response to IL-2. Several investigators have proposed that the increased endothelial expression of ICAM-1 induced by IL-2 treatment may result in lymphocyte margination and contribute to the lymphopenia characteristic of IL-2-treated patients. In addition to its suppressive effect on IL-2–induced TNF synthesis, dexamethasone inhibits the increase in ICAM-1 expression that would otherwise occur in cultured fibroblasts on exposure to inflammatory cytokines. These results predict that dexamethasone administration should prevent the diffuse endothelial activation and the lymphopenia induced by IL-2 treatment by inhibiting both the release of TNF and possibly its biological effects on endothelial cells. Despite these considerations, steroid administration did not prevent the precipitous decline in circulating lymphocytes after an IL-2 injection. We therefore obtained skin biopsy samples for immunohistochemical analysis from four patients undergoing treatment with IL-2/Dex at the MTD. Endothelial expression of ELAM-1 was detected in three of the four biopsy samples examined (data not shown), clearly indicating that dexamethasone does not consistently suppress IL-2–induced expression of ELAM-1. There are several plausible explanations for this finding. For example, endothelial activation in the IL-2/Dex patients could occur as a consequence of circulating IL-2–induced cytokines other than those specifically assayed in this investigation or as a consequence of the local production of cytokines that may not be reflected in the circulation. The latter alternative is especially attractive, because both vascular smooth muscle and endothelial cells are abundant sources of various cytokines that could result in endothelial activation. Alternatively, it is possible that neutrophil chemotaxis, hepatic CRP synthesis, endothelial cell activation, and the TNF RIA are not equally sensitive indicators of circulating TNF and that the release of TNF in amounts that yield plasma concentrations below the threshold of detectability for the RIA and inadequate to stimulate hepatic CRP synthesis may be sufficient to induce the slight decrement in neutrophil chemotaxis and the endothelial expression of ELAM-1 observed in patients treated with IL-2/Dex.

We and others have demonstrated that endothelial cells can be lysed by IL-2–activated PBMCs in vitro and have conjectured that IL-2–induced capillary leak may be due in part to direct cell-mediated injury of the endothelium. Recent work by Peace et al showing that IL-2–associated morbidity is largely prevented by NK cell depletion supports this view. Steroids inhibit LAK cell induction in vitro and it is possible that their ability to reduce IL-2–associated capillary leak may be partly due to the suppression of LAK cell induction and LAK cell–mediated endothelial injury rather than the inhibition of TNF synthesis. On the other hand, CD16+ lymphocytes (the predominant LAK cell precursors in peripheral blood) produce TNF when stimulated with IL-2 (unpublished observation), suggesting that the palliative effect of NK cell depletion on capillary leak could be due to a reduction in IL-2–induced TNF synthesis by these cells.

Three patients participating in this study (all of whom received IL-2 at a dose of 1.8 × 10^6 IU/kg) had some degree of tumor regression. In fact, one patient with renal cell carcinoma achieved a 75% reduction in the size of his metastatic pulmonary nodules. Although LAK cell induction by IL-2 is strongly inhibited by steroids, Grimm has shown that cytotoxic T lymphocyte induction with allogeneic targets is relatively steroid resistant. Moreover, steroids have little effect on target cell lysis by CTL. It is therefore possible that the antineoplastic effect of the IL-2/Dex combination may have been secondary to the activation of tumor-specific cytotoxic T lymphocytes (CTL) by IL-2.

This investigation provides additional information linking the increased serum hepatic acute phase protein levels, the recently described neutrophil chemotactic defect, and several of the life-threatening side effects induced by IL-2 administration to the release of TNF and other secondary cytokines. Our results suggest that it may be possible to suppress the release of TNF with dexamethasone and thereby reduce the toxicity of IL-2 without completely abrogating its antineoplastic activity. This premise requires confirmation in phase II clinical trials.

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EFFECTS OF DEXAMETHASONE ON IL-2 TOXICITY

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Inhibition of interleukin-2-induced tumor necrosis factor release by dexamethasone: prevention of an acquired neutrophil chemotaxis defect and differential suppression of interleukin-2-associated side effects [see comments]

JW Mier, G Vachino, MS Klempner, FR Aronson, R Noring, S Smith, EP Brandon, W Laird and MB Atkins