Characteristics and Requirements of the Interaction Between Human Monocytes and Tumor Cells on the Single Cell Level

By Marc G. Golightly, Dina G. Fischer, Christer Ohlander, and Hillel S. Koren

Highly purified (97%-99%) and viable (99%) peripheral blood monocytes obtained by EDTA-reversible adherence to autologous-serum-precoated plastic surfaces could rapidly lyse a variety of tumor cells in a 3-4-hr ⁵¹Cr release assay. Using these monocytes as effectors, a short-term agarose/conjugate assay was utilized, permitting us to examine the interaction between fresh human monocytes and neoplastic target cells on a single cell level. That the tumor-bound effector cells were indeed monocytes was confirmed by employing the monocyte-specific monoclonal antibody 61D3, which stained 95%-99% of the mononuclear cells bound to conjugated and killed K562 tumor targets. The binding of monocytes to target cells appeared to be temperature dependent and was extremely rapid, reaching a plateau after 5 min at 30°C. Our findings demonstrated for the first time that only a proportion of human blood monocytes can bind to a particular target cell and that only a fraction of the binding cells have the intrinsic potential to kill those neoplastic targets. The proportion of monocytes capable of binding and killing varies between individuals and also depends on the tumor cell used, indicating heterogeneity in the monocyte and tumor cell populations. The highest proportion of monocytes bind to the human erythromyeloid leukemia K562 cell line (13%-50%). The frequency of monocytes capable of killing K562 tumor cells is relatively low (7%-13%). The system described here should be useful to study the heterogeneity of mononuclear phagocytes and to analyze the molecular basis of the interaction between those effector cells and neoplastic target cells.

MATERIALS AND METHODS

Monocyte Isolation

The novel technique for the isolation of monocytes from peripheral blood has been previously described. Recently, human peripheral blood monocytes were shown by several investigators to exhibit spontaneous cytotoxicity against various tumor targets using long-term isotope release assays (16-72 hr). The lysis by mononuclear phagocytes of target cells has so far been found to require intimate cell contact in the guinea pig and in the mouse. Furthermore, the binding of activated murine macrophages to tumor cells was shown to be necessary to initiate lysis. Using a new methodology for isolation of highly purified (97%-99%) human peripheral blood monocytes, we were recently able to demonstrate their ability to lyse tumor cells spontaneously in a short-term (3-4 hr) ⁵¹Cr release assay. In this article we have established the conditions and kinetics of the binding to and killing of tumor cells by blood monocytes at the single cell level. Furthermore, our findings demonstrate that the ability to bind and lyse a particular tumor cell is characteristic for a subpopulation of monocytes, indicating their heterogeneity.

Target Cells

The following suspension cell lines were used for targets: P815, a mouse mastocytoma line; CEM, a human T-cell line; and K562, a human myeloid cell line. The cells were maintained in RPMI-FBS medium. The cell lines were mycoplasma free as determined periodically by the fluorescent staining method.

Monocyte Conjugation/Agarose Assay

The technique of Bradley and Bonavida, with modifications necessary for monocytes, was employed to examine spontaneous monocyte cytotoxicity on a single cell level. For each assay, 0.25 x 10⁶ freshly isolated monocytes were added to 0.25 x 10⁶ target cells (total volume 0.5 ml in RPMI-FBS) in Eppendorf 1.5 ml polypropylene microcentrifuge tubes (Brinkman Instruments, Inc. Westbury, N.Y.). To further reduce adherence and clumping, the cell suspension was immediately centrifuged at 200 g for 5 min. The pellet was then incubated at 30°C for 10 min, followed by 20 min at 4°C. After 3-4 min at room temperature, most of the supernatant...
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was removed and the pellet was gently resuspended in 100 μl. Fifty microliters of this cell suspension were added to 100 μl of molten 0.5% agarose at 39°C (Seakem agarose, Marine Colloids Inc. Rockland, Me.) and then plated on microscope slides that had been precoated with agarose and dried over an open flame. The slides were then covered with RPMI-FBS in 100-mm tissue culture dishes, and incubated 3–4 hr at 37°C in 5% CO₂ humidified air, unless otherwise stated. Incubation in 0.3% trypan blue for 10 min was used to stain dead cells. Excess stain was removed by washing in PBS, and the cells were fixed in 0.37% formaldehyde. The slides were then scored for the percent bound monocytes and the present dead conjugated target cells.

Calculations and Statistics

In each slide, 200 effectors were counted to determine the percent bound effectors, and 100–200 conjugates were counted to determine percent dead conjugated targets. The calculations for the conjugate assay were performed as follows:

Percent bound monocytes = \[ \frac{\text{No. of bound monocytes}}{\text{Total no. of monocytes}} \times 100 \]

Percent dead conjugated targets cells = \[ \frac{\text{No. of dead conjugated targets}}{\text{Total no. of conjugated targets}} \times 100 \]

Percent cytotoxic monocytes = \[ \frac{\text{Percent bound monocytes} \times \text{Percent dead conjugated targets}}{100} \]

The percent cytotoxic monocytes provides an estimate of the proportion of total monocytes that lysed a tumor target cell. Conjugate slide preparations were used only when unbound dead targets constituted less than 2% of the total. The standard error of the percent bound monocytes and the present dead conjugated targets was determined by \[ \sqrt{\frac{P(1-P)}{\text{Total number of conjugated targets}}} \times \sqrt{\frac{1}{n}} \] where \( P \) is the proportion of bound monocytes or dead conjugated targets, and \( n \) is the total number of monocytes or conjugated targets counted. The standard error of the percent cytotoxic monocytes is approximated by the method of statistical differentials.

\(^{51}\)Cr Release Cytotoxicity Assay

Target cells (5–10 × 10⁶) were labeled with Na₂\(^{51}\)CrO₄ (New England Nuclear, Boston, Mass.) as previously described. All assays were carried out in triplicate in conical wells of microtiter plates in a total volume of 0.2 ml of RPMI-FBS. Each well received 10⁴ targets, and the monocytes were added at appropriate concentrations to obtain the various effector cell/target cell ratios (EC/TC). The microtiter plates were centrifuged 3 min at 80 g and incubated for 3 hr at 37°C in a humidified 5% CO₂ incubator. To terminate the assay, plates were centrifuged for 5 min at 500 g and 100 μl of supernatant removed from each well for counting in a well-type gamma counter (Searle, Model 1185).

Calculations

Percent specific lysis in all experiments was calculated according to the following formula:

Percent specific lysis = \[ \frac{\text{Experimental cpm} - \text{Control cpm}}{\text{Maximum cpm} - \text{Control cpm}} \times 100 \]

The maximum release was determined by adding 0.5% Triton X-100 to an aliquot of target cells. Control release is defined as the cpm released from target cells incubated with medium alone: this value was usually 5%–10% of maximum. Adding 10⁴ unlabeled targets to control wells reduced the spontaneous release and was required in experiments in which the incubation exceeded 4 hr.

Variability of Binding and Killing in Conjugate/Agarose Assay

The majority of the variation that occurs in the conjugate/agarose assay results from donor-to-donor variation and not experimental variation. The values for 10 healthy donors in 29 experiments over a period of 9 mo ranged from 13% to 50% bound monocytes and 6%–45% killed conjugated K562 targets. The mean ± standard error for binding and killing for all 29 experiments was 29.4% ± 2.6% and 21.1% ± 2.6%, respectively. The range of binding and killing of K562 targets for individual donors tested on separate days was low. For instance, the values for one donor tested on six occasions ranged from 23% to 36% binding (30.5% ± 2.3% mean) and 14%–28% killing (21.8% ± 2.1% mean).

Cytocentrifuge Preparation of Monocyte-Target Cell Conjugates

The conjugate suspension diluted in RPMI-FBS was centrifuged onto slides at a low speed (5 min at 800 rpm) in a cytocentrifuge (Cytospin, Shandon Southern), then stained with Kaplow’s peroxidase stain.

Fluorescence Staining of Conjugates with Monoclonal Antibodies

Conjugates of monocytes and K562 tumor cells were formed as described above and subsequently resuspended in medium containing 10% dextran T500 (Pharmacia Fine Chemicals, Uppsala, Sweden) according to the method described by Martz. For control, large granular lymphocytes (LGL) isolated by Percoll (Pharmacia) density centrifugation were conjugated with K562 targets and set up in parallel. After incubation of the conjugates for 3–4 hr at 37°C, the cells were spun, washed with PBS + 2% BSA + 0.02% NaN₃, and stained for immunofluorescence with monoclonal antibodies using standard procedures.

Two murine monoclonal antibodies were used: 61D3 (BRL, Gaithersburg, Md.), shown to be highly specific for monocytes, and OKT10 (kindly provided by Dr. John Ortaldo, NIH), demonstrated to be specific for LGL in human peripheral blood. An affinity-purified and fluoresceinated (F/P-6) goat anti-mouse IgG (Tago Inc., Burlingame, Calif.) was used to visualize the binding of the monoclonal antibodies to the mononuclear cells. This reagent was found not to stain monocytes or LGL directly (data not shown).

RESULTS

Identification of the Tumor-Bound Effector Cells

The cells binding the tumor target cells were shown to be monocytes. Of the cells that were bound to the targets, 93%–99% were peroxidase positive (Table 1) and had morphological characteristics of monocytes. Moreover, when the monoclonal antibody 61D3, specific for monocytes, was employed, the data clearly demonstrated that 96%–99% of the cells bound to K562 targets were monocytes and that an identical proportion of monocytes were found bound to dead conjugated K562 cells (Table 1). Fewer than 2% of the
out the initial 10-mm incubation in all subsequent experiments at 30°C to possibly minimize target killing prior to immobilization in agarose.

Early Time Course of Tumor Cell Binding and Killing by Monocytes

In order to establish the optimal incubation time required for maximal binding, the cell pellets were incubated at 30°C for various times before the conjugates were immobilized in agarose. The data of a representative experiment (Fig. 1) show that binding of monocytes to K562 occurred rapidly (23% after 2.5 min) and reached nearly maximal levels (41%) after 5 min. The percent dead conjugated targets after 3 hr at 37°C were similar for all of the tested time points, indicating that those monocytes that bound tumor cells very quickly (i.e., <2.5 min at 30°C) had the same cytotoxic ability as those that underwent a longer preincubation time at 30°C. While a 5 or 10-min incubation at 30°C resulted in maximal binding (41% and 44%, respectively), few lysed targets (3% and 5%) were found immediately after conjugation without further incubation at 37°C. Hence, the additional experiments at 30°C to possibly minimize target killing prior to immobilization in agarose.

Table 2. Temperature Dependence of Monocyte Binding

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Percent Bound Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°C</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>5°C</td>
<td>5.0 ± 1.5</td>
</tr>
<tr>
<td>10°C</td>
<td>5.7 ± 1.3</td>
</tr>
<tr>
<td>20°C</td>
<td>11.7 ± 1.8</td>
</tr>
<tr>
<td>30°C</td>
<td>18.5 ± 2.7</td>
</tr>
<tr>
<td>37°C</td>
<td>21.9 ± 2.8</td>
</tr>
</tbody>
</table>

*After the initial incubation at the various temperatures stated, the conjugate slides were incubated for 3 hr at 37°C followed by staining with trypan blue.
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Fig. 2. Monocyte–tumor cell conjugates in agarose after 3 hr at 37°C. (A) Monocyte bound to a trypan blue positive K562 target cell. (B) Monocyte bound to a viable K562 target cell.

incubation of the conjugates at 37°C was required to achieve lysis of the monocyte-bound targets. A micrograph of binding and lysis of K562 targets by fresh blood monocytes in the agarose assay is demonstrated in Fig. 2.

The Effect of Cell Concentration on Binding, Killing, and Monocyte–Tumor Cell Configuration

When more than one monocyte is bound to a lysed tumor cell, it is difficult to determine how many of the bound effectors have cytolytic activity. In order to estimate the proportion of cytotoxic monocytes it was necessary to establish the optimal effector cell:target cell (EC:TC) ratio that yielded the most singlet configurations (one monocyte bound to one target cell) while still maintaining high binding levels. The monocyte concentration was varied, while the target cell number was kept constant (Table 3); then, in another separate experiment, the target cell concentration was varied while the monocyte was kept constant (Table 4). The configuration of the conjugates was scored in addition to binding and killing.

As the proportion of monocytes was increased from 1:1 to 8:1, the percent bound monocytes decreased slightly, with no significant change in the percentage of killed conjugated targets (Table 3). The decrease in binding at the higher EC:TC ratios may have resulted from crowding and steric hindrance. An EC:TC ratio of 1:1 was found to yield the highest proportion of conjugates with singlet configuration within the EC:TC range (Table 3) tested.

Increasing the target cell concentration (1:1 to 1:8) did not affect binding levels (Table 4); however, at the higher tumor cell concentrations (1:4 and 1:8), a marked decrease in the ability of the bound monocytes to kill the targets was observed. An EC:TC ratio of 1:1 yielded the most singlet configurations within the target cell concentrations tested in Table 4.

Since maximal binding and killing and the highest proportion of singlet conjugate configurations were scored at a 1:1 EC:TC ratio, this ratio was used in all further experiments.

Kinetics of Monocyte-Mediated Target Cell Killing in Agarose and 51Cr Release Assays

The kinetics of tumor cell lysis by monocytes in agarose and 51Cr release assays were compared. Figure 3 demonstrates maximal target cell killing in the agarose assay after 4 hr at 37°C, although in other experiments, peak activity was often reached by 3 hr (data not shown). In all experiments the killing in the agarose assay after 20 hr was either at or below the plateau level. In the experiment presented in Fig. 3, the 20-hr value was 27%. However, on several occasions, the values of trypan-blue-positive conjugated targets dropped below the plateau levels after 20 hr incubation. This is probably due to the inability of severely

Table 3. The Effect of Monocyte Concentration on Binding and Killing of Tumor Cells (K562)

<table>
<thead>
<tr>
<th>Effector:Target Ratio*</th>
<th>Bound Monocytes (%)</th>
<th>Conjugated Targets (%)</th>
<th>Cytotoxic Monocytes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 1:1</td>
<td>42 ± 3.5</td>
<td>22 ± 4.1</td>
<td>9.2 ± 1.9</td>
</tr>
<tr>
<td>2:1</td>
<td>35 ± 3.4</td>
<td>20 ± 4.0</td>
<td>7.0 ± 1.5</td>
</tr>
<tr>
<td>4:1</td>
<td>29 ± 3.2</td>
<td>28 ± 4.5</td>
<td>8.0 ± 1.6</td>
</tr>
<tr>
<td>8:1</td>
<td>29 ± 3.2</td>
<td>23 ± 4.2</td>
<td>6.7 ± 1.4</td>
</tr>
<tr>
<td>B. 1:1</td>
<td>3</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>2:1</td>
<td>8</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>4:1</td>
<td>12</td>
<td>26</td>
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<tr>
<td>8:1</td>
<td>13</td>
<td>31</td>
<td>49</td>
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Conjugate Configuration†

<table>
<thead>
<tr>
<th>Effector:Target Ratio</th>
<th>3E/1T</th>
<th>2E/1T</th>
<th>1E/1T</th>
<th>1E/2T</th>
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</thead>
<tbody>
<tr>
<td>B. 1:1</td>
<td>3</td>
<td>12</td>
<td>68</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>2:1</td>
<td>8</td>
<td>23</td>
<td>58</td>
<td>10</td>
<td>1</td>
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<tr>
<td>4:1</td>
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<td>13</td>
<td>31</td>
<td>49</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

*0.25 x 10⁶ Target cells were added to the appropriate number of effectors to yield the given EC:TC ratios. The total volume was 0.5ml.
†Conjugate configurations are expressed as percentages of total conjugated counted. 3E/1T = 3 or more effectors per target, 1E/3T = one effector bound by 3 or more targets.
Table 4. The Effect of Target Cell Concentration on Binding and Killing of Tumor Cells (K562)

<table>
<thead>
<tr>
<th>Effector:Target Ratio*</th>
<th>Dead Conjugated Targets (%)</th>
<th>Cytotoxic Monocytes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 1:1</td>
<td>14.0 ± 2.5</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>1:2</td>
<td>14.5 ± 2.5</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>1:4</td>
<td>7.5 ± 1.9</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td>1:8</td>
<td>4.5 ± 1.5</td>
<td>1.5 ± 0.4</td>
</tr>
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</table>

Conjugate Configuration†

<table>
<thead>
<tr>
<th>Effector:Target Ratio</th>
<th>3E/1T</th>
<th>2E/1T</th>
<th>1E/1T</th>
<th>1E/2T</th>
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<tbody>
<tr>
<td>A. 1:1</td>
<td>3</td>
<td>12</td>
<td>78</td>
<td>7</td>
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<tr>
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<td>1</td>
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<tr>
<td>1:4</td>
<td>3</td>
<td>7</td>
<td>69</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>1:8</td>
<td>6</td>
<td>6</td>
<td>68</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

*0.25 x 10⁶ effector cells were combined with the appropriate number of target cells to yield the given ratios.
†Conjugate configurations are expressed as percentages of total conjugates counted. 3E/1T = 3 or more effectors per target, 1E/3T = one effector bound by 3 or more targets.

damaged conjugated targets to take up trypan blue. There was a good accordance in detecting lysis of tumor targets using these two independent techniques at the given EC:TC. However, ¹⁰⁵Cr release continued to rise over a longer period of time (6–9 hr), whereas the lysis in the agarose assay plateaued after 3–4 hr.

Target Cell Binding and Sensitivity to Killing by Monocytes

The sensitivity of various tumor target cells to killing by monocytes was determined both by the single cell conjugate cytotoxicity assay and by the ⁵¹Cr release assay. A representative experiment (Fig. 4) demonstrated that a high proportion of the monocytes (50.5%) were bound to the K562 targets, and that 31% of these monocytes also killed the bound targets. Two other tumor targets, CEM and P815, were bound only by a small percent of the monocytes (12% and 13.5%, respectively). However, a relatively high proportion of the bound CEM targets were lysed (43%), while P815 was insensitive to lysis.

The calculation of the proportion of monocytes from the total monocyte population that were able to kill each target (percent cytotoxic monocytes) demonstrated that K562 was the most sensitive target and P815 the most resistant, in accordance with the data obtained from the ⁵¹Cr release assay (Fig. 4).

DISCUSSION

We have previously reported that human monocytes freshly isolated by a novel technique can rapidly lyse tumor target cells in a 3-hr ⁵¹Cr release assay.¹² No

Fig. 3. The kinetics of monocyte-mediated target cell lysis. The percent dead conjugated targets (○) in the agarose assay and the percent specific ⁵¹Cr release (●) in the chromium release assay were determined after various times (1–7 hr) at 37°C.

Fig. 4. Target cell binding and sensitivity to lysis by monocytes. K562, CEM, and P815 target cells were examined in the conjugate-agarose assay and the ⁵¹Cr release assays. The percent bound monocytes, dead conjugated targets, and cytotoxic monocytes from the conjugate-agarose assay are shown for the various targets in the box on the left. The data from the ⁵¹Cr release assay for the different targets is shown in the box on the right.
evidence for the involvement of soluble recognition factors was obtained in our system. A Fab anti-human F(ab')2 reagent was unable to inhibit the spontaneous killing by monocytes, but obliterated the antibody-dependent cellular cytotoxicity by the same monocyte population against a tumor target cell. Using the conjugate/agarose technique, we have studied the interaction between these freshly isolated peripheral blood monocytes and tumor target cells in the single cell level. Morphological observations and peroxidase stains provided strong evidence that the effector cells were monocytes. Further and definitive evidence demonstrating the identity of the effector cells as monocytes, and ruling out the involvement of natural killer cells in our system, was provided by experiments utilizing a monocyte-specific monoclonal antibody (61D3) (Table 1). In the conjugate/agarose assay, 13%-50% of freshly isolated monocytes from 10 healthy volunteers (29 experiment) were found to bind K562 targets, while 6%-45% of the monocytes that bound also had the capacity to kill the target cell.

The binding of monocytes to target cells appeared to be temperature dependent, since binding decreased at temperatures lower than 30°C. Very little binding occurred at 0°C.

The binding of target cells by monocytes was extremely rapid, with half-maximal binding after 2.5 min, reaching a plateau after 5 min at 30°C. Substantial amounts of lysis occurred only if the conjugates were further incubated at 37°C (Fig. 1), suggesting that lysis is a multistep phenomenon, as previously suggested in murine systems. Similar binding kinetics were described for human NK lymphocytes and mouse cytotoxic T cells, while BCG-activated mouse macrophages were found to require a longer time (60-75 min) for maximum binding. The differences in the binding kinetics could be due to differences in the species, in the state of activation of the effector cell populations, or in the binding assays.

Maximal binding and killing were demonstrated at an EC:TC of 1:1. In addition, this ratio was found optimal for obtaining conjugates with one monocyte and one tumor cell (singlet configuration). The finding that excess target cells causes a reduction in the number of conjugated dead tumor cells is intriguing and does not appear to be due to steric interference, since high concentrations of tumor cells inhibit the killing even when added to preformed conjugates already immobilized an agarose (data not shown).

Having investigated the conditions required for the binding and killing by fresh blood monocytes, we then examined the kinetics of lysis and found a good accordance between both the agarose and the 51Cr release assays (Fig. 3). The finding that target cell lysis in the agarose assay reached a maximum after 3-4 hr, while 51Cr release continued to rise, is probably due to the immobilizations of the cells in the agarose preventing them from killing multiple targets.

Though the cytotoxicity values (percent cytotoxic monocytes and percent specific lysis) obtained in both assays correlate very well, the single cell assay provided novel information unattainable from a 51Cr release assay. Specifically, the conjugate experiments have shown that while a considerably higher proportion of monocytes bind to K562 than to CEM or P815 targets, the percent of dead conjugated CEM was at least as high as that with K562 and considerably higher than with P815. These findings demonstrate that (A) the capacity of monocytes to bind to a given tumor does not necessarily correlate with the ability to kill, (B) CEM is more sensitive to lysis (discounting binding) than K562 or that there is less nonspecific binding in the CEM, (C) P815 is almost totally resistant to lysis even though it binds a small but similar proportion of monocytes as CEM targets do.

Taken together, the data imply that the differences in the levels of binding and killing manifest a previously undescribed aspect of monocyte heterogeneity detected at the single cell level. Qualitative and/or quantitative variations in the expression of putative target determinants may also contribute to the observed differences in the binding and killing by the monocytes.

Experiments designed to separate conjugates of tumor cells and monocytes from unbound monocytes, currently performed in our laboratory, may be useful to determine whether tumor binding is a definitive marker of a subpopulation of monocytes or a transient property associated with a particular step in the monocyte maturation pathway.

ACKNOWLEDGMENT

We would like to thank Drs. Adams and Jensen for helpful discussions and Drs. Herberman and Ortaldo for critical comments in the preparation of this manuscript; C. Phillip Brandt for his technical assistance; Dr. Deborah Dawson for her assistance in statistical evaluations; and Connie Hayes and Lu Ann W. Smith for their secretarial assistance.

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