Chronic oral anticoagulation treatment has been used for the prevention of thromboembolic events for more than 6 decades. The main indications for oral anticoagulant treatment are deep venous thrombosis, atrial fibrillation, and prosthetic valves. For prevention of thromboembolic events, without increasing the risk of minor or major bleeding, frequent monitoring and dose adjustment of the anticoagulant treatment is necessary. In a high percentage of cases, anticoagulant treatment would be contraindicated, for example, in patients with an obviously greater risk of hemorrhage than of thromboembolism. The uremic patients present an increased risk of hemorrhage due to vessel wall and platelet abnormalities and the presence of factors that inhibit the normal platelet adhesion and aggregation mechanisms. However, oral anticoagulant therapy is not considered automatically contraindicated in uremic hemodialyzed patients.1,2 Moreover, the clinical use of vitamin K antagonists as anticoagulants has been related, not only with the high risk of bleeding, but also with low bone mineral density and increased risk of fracture. Vitamin K dependent proteins not only regulate blood coagulation but also other physiological processes such as bone metabolism, vascular calcification, cell growth, and apoptosis, and can lead to unexpected side effects.3-6-8-10 In this study, 4 uremic hemodialyzed patients who received oral anticoagulation treatment and presented with bone fracture are described. The association between coumarins derivatives and bone damage is analyzed.

Patient Description

In our renal unit about 140 uremic hemodialyzed patients are treated. From these patients, 11 are undergoing oral anticoagulant treatment. Over the last 2 years, 5 patients presented with bone fracture and 4 of them were undergoing oral anticoagulant treatment (acenocoumarol 1 mg daily). The dose was modified according to international normalized ratio (INR) units. The use of vitamin K antagonists as an anticoagulant has been considered a cause of bleeding and is related to low bone mineral density and a high risk of fracture. In our data, the number of patients who receive oral anticoagulants (11 patients) and the number of them who present with bone fracture (4 patients) raises the suspicion that there is an association between anticoagulant treatments and bone fractures.

Discussion

Oral anticoagulation therapy is recommended in patients with an elevated risk of
Clinical Perspectives

Clot formation. The most common indications for oral anticoagulation treatment are atrial fibrillation, deep venous thrombosis, and prosthetic valves. However, oral anticoagulation therapy is often underused because of a fear of bleeding occurring due to over-anticoagulation and to some other serious complications, especially in elderly patients.1,2,7

Clinicians know that the use of coumarins decreases the tendency of blood to clot by the inhibition of the vitamin K dependent γ-carboxylation of clotting factors (II, VII, IX, X). However, the clinical use of vitamin K antagonists has been related to low bone mineral density and increased risk of fracture.4-6

In published studies, there have been discrepancies in the results found on the effects of vitamin K antagonists on bone.4-6 The disagreement is whether the high fracture risk is due to a direct pharmacological effect or due to the disease necessitating treatment. The majority of the data suggests that vitamin K antagonists exert harmful effects on bone.5-6

Poor vitamin K status must be regarded as a serious risk factor for increased post-menopausal bone loss and for artery calcification, especially in diabetes, end-stage renal failure, and aging. The specific role of vitamin K in bone metabolism is not well defined, so the consequences of

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Main characteristics of the study patients (n = 4).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Duration of HD (months)</td>
<td>43</td>
</tr>
<tr>
<td>Last year mean value of:</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.6</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>4.2</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>640</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>35</td>
</tr>
<tr>
<td>Alk. phosphatase</td>
<td>206</td>
</tr>
<tr>
<td>Calciphylaxis</td>
<td>Yes</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>Lumbar vertebra</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>+</td>
</tr>
<tr>
<td>Valve prosthetic</td>
<td>–</td>
</tr>
<tr>
<td>Medication</td>
<td>EPO</td>
</tr>
<tr>
<td></td>
<td>Insulin Acenocoumarol Paricalcitol Cinacalcet Sodium Thiosulfate Phosphate binders Vitamins B Carnitine</td>
</tr>
</tbody>
</table>

Hct, hematocrit; PTH, parathyroid hormone

TABLE I. Main characteristics of the study patients (n = 4).
Clinical Perspectives

oral anticoagulant use on bone quality are also unclear. Interestingly, coumarin derivatives inhibit the action of vitamin K for \( \gamma \)-carboxylation of osteocalcin and matrix Gla-protein (MGP). The non-carboxylated osteocalcin cannot bind calcium effectively and under-carboxylated MGP has been associated with arterial calcification. Studies have demonstrated that subjects on long-term oral anticoagulant treatment have more significant arterial and heart valve calcification than the control population. In addition, vitamin K might directly reduce bone resorption due to decreased prostaglandin E2 synthesis and osteoclast-like cell formation, while vitamin K treatment has been shown to decrease urinary excretions of hydroxyproline which is a marker of bone resorption in post-menopausal women.1.4-8

The clinical characteristics of our 4 hemodialysed patients with bone fracture, are as follows: Patients were exposed to oral anticoagulation for more than 2 years; are uremic hemodialysed; and elderly. As mentioned above, these categories of patients present poor vitamin K status. By consensus, the dose of coumarin derivatives was decreased to approximately 50% in octogenarians in comparison to younger patients.

Patients with end-stage renal failure have been found to be at an increased risk for bone fracture and low mineral density. Of the hemodialysed uremic patients, 5% to 10% receive oral anticoagulants.2.3.7.9 Moreover, a high number of uremic hemodialysed patients were found to have low serum vitamin K and this is associated with increased bone fractures and elevated intact parathyroid hormone. Very little vitamin K is stored in the body because it is metabolized in the liver. So, dietary deficiency and comorbidities of ageing and uremic patients may lead to vitamin K depletion. All these factors may contribute to a high risk of bone fracture.5.10.11

Some reports suggest that vitamin K supplementation in patients undergoing oral anticoagulant treatment should improve the stability of anticoagulation properties and protect the patient from bone damage and arterial calcification.4.8.11.12.20.4-7 Vitamin K may also play a protective role against age-related bone loss. In Japan, the incidence of hip fracture is lower than in Europe and United States. One explanation may be that the Japanese consume natto, a food very rich in menaquinone-7 (K2).13.20.4-7

In conclusion, uremic hemodialysed patients may present serious complications when treated with coumarin-derived anticoagulants. The main complications are hemorrhage, increased risk for bone fracture, and a high prevalence of arterial calcification with calciphylaxis. Before the recommendation of these drugs to uremic and elderly patients a rigorous evaluation of the risks versus benefits is needed, in order to optimize patient selection for the safe use of oral anticoagulant therapy.

References

8. Binkley NC, Krueger DC, Edelge JA, et al. Vitamin K supplementation reduces serum concentrations of under-
AQ5: Change as meant?
AQ6: Change as meant?
AQ7: Change as meant?
AQ8: Change as meant?
READ PROOFS CAREFULLY

- This will be your only chance to review these proofs.
- Please note that the volume and page numbers shown on the proofs are for position only.

ANSWER ALL QUERIES ON PROOFS (Queries for you to answer are attached as the last page of your proof.)

- Mark all corrections directly on the proofs. Note that excessive author alterations may ultimately result in delay of publication and extra costs may be charged to you.

CHECK FIGURES AND TABLES CAREFULLY (Color figures will be sent under separate cover.)

- Check size, numbering, and orientation of figures.
- All images in the PDF are downsampled (reduced to lower resolution and file size) to facilitate Internet delivery. These images will appear at higher resolution and sharpness in the printed article.
- Review figure legends to ensure that they are complete.
- Check all tables. Review layout, title, and footnotes.

COMPLETE REPRINT ORDER FORM

- Fill out the attached reprint order form. It is important to return the form even if you are not ordering reprints. You may, if you wish, pay for the reprints with a credit card. Reprints will be mailed only after your article appears in print. This is the most opportune time to order reprints. If you wait until after your article comes off press, the reprints will be considerably more expensive.

RETURN PROOFS

RETURN WITHIN 48 HOURS OF RECEIPT VIA FAX TO 781-388-0507

QUESTIONS?

Mrs. Samara Kuehne, Editor
Phone: 818-908-0287(direct)
E-mail: skuehne@wiley.com
Refer to journal acronym and article production number (i.e., DAT 00-001 for Dialysis & Transplantation Education ms 00-001).
COPYRIGHT TRANSFER AGREEMENT

Date: ____________________ Contributor name: ____________________

Contributor address: __________________________________________________________

Manuscript number (Editorial office only): _________________________________________

Re: Manuscript entitled ________________________________________________________ (the "Contribution")

for publication in ____________________________________________________________ (the "Journal")

published by _________________________________________________________________ ("Wiley-Blackwell").

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable Wiley-Blackwell to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement signed and returned as directed in the Journal's instructions for authors as soon as possible. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void. **Publication cannot proceed without a signed copy of this Agreement.**

### A. COPYRIGHT

1. The Contributor assigns to Wiley-Blackwell, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to publish, republish, transmit, sell, distribute and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so.

2. Reproduction, posting, transmission or other distribution or use of the final Contribution in whole or in part in any medium by the Contributor as permitted by this Agreement requires a citation to the Journal and an appropriate credit to Wiley-Blackwell as Publisher, and/or the Society if applicable, suitable in form and content as follows: (Title of Article, Author, Journal Title and Volume/Issue, Copyright © [year], copyright owner as specified in the Journal). Links to the final article on Wiley-Blackwell's website are encouraged where appropriate.

### B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor's Employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution.

### C. PERMITTED USES BY CONTRIBUTOR

1. **Submitted Version.** Wiley-Blackwell licenses back to the Contributor the following rights with respect to the final published version of the Contribution:

   a. Copies for colleagues. The personal right of the Contributor only to send or transmit individual copies of the final published version in any format to colleagues upon their specific request provided no fee is charged, and further-provided that there is no systematic distribution of the Contribution, e.g. posting on a listserve, website or automated delivery.

   b. Re-use in other publications. The right to re-use the final Contribution or parts thereof for any publication authored or edited by the Contributor (excluding journal articles) where such re-used material constitutes less than half of the total material in such publication. In such case, any modifications should be accurately noted.

   c. Teaching duties. The right to include the Contribution in teaching or training duties at the Contributor's institution/place of employment including in course packs, e-reserves, presentation at professional conferences, in-house training, or distance learning. The Contribution may not be used in seminars outside of normal teaching obligations (e.g. commercial seminars). Electronic posting of the final published version in connection with teaching/training at the Contributor's institution/place of employment is permitted subject to the implementation of reasonable access control mechanisms, such as user name and password. Posting the final published version on the open Internet is not permitted.

   d. Oral presentations. The right to make oral presentations based on the Contribution.

2. **Accepted Version.** Re-use of the accepted and peer-reviewed (but not final) version of the Contribution shall be by separate agreement with Wiley-Blackwell. Wiley-Blackwell has agreements with certain funding agencies governing reuse of this version. The details of those relationships, and other offerings allowing open web use, are set forth at the following website: http://www.wiley.com/go/funderstatement. NIH grantees should check the box at the bottom of this document.

### 3. Final Published Version.** Wiley-Blackwell hereby licenses back to the Contributor the following rights with respect to the final published version of the Contribution:

   a. Copies for colleagues. The personal right of the Contributor only to send or transmit individual copies of the final published version in any format to colleagues upon their specific request provided no fee is charged, and further-provided that there is no systematic distribution of the Contribution, e.g. posting on a listserve, website or automated delivery.

   b. Re-use in other publications. The right to re-use the final Contribution or parts thereof for any publication authored or edited by the Contributor (excluding journal articles) where such re-used material constitutes less than half of the total material in such publication. In such case, any modifications should be accurately noted.

   c. Teaching duties. The right to include the Contribution in teaching or training duties at the Contributor's institution/place of employment including in course packs, e-reserves, presentation at professional conferences, in-house training, or distance learning. The Contribution may not be used in seminars outside of normal teaching obligations (e.g. commercial seminars). Electronic posting of the final published version in connection with teaching/training at the Contributor's institution/place of employment is permitted subject to the implementation of reasonable access control mechanisms, such as user name and password. Posting the final published version on the open Internet is not permitted.

   d. Oral presentations. The right to make oral presentations based on the Contribution.

### 4. Article Abstracts, Figures, Tables, Data Sets, Artwork and Selected Text (up to 250 words).

   a. Contributors may re-use unmodified abstracts for any non-commercial purpose. For on-line uses of the abstracts, Wiley-Blackwell encourages but does not require linking back to the final published versions.

   b. Contributors may re-use figures, tables, data sets, artwork, and selected text up to 250 words from their Contributions, provided the following conditions are met:

      (i) Full and accurate credit must be given to the Contribution.

      (ii) Modifications to the figures, tables and data must be noted. Otherwise, no changes may be made.

      (iii) The reuse may not be made for direct commercial purposes, or for financial consideration to the Contributor.

      (iv) Nothing herein shall permit dual publication in violation of journal ethical practices.

---

CTA-A
**D. CONTRIBUTIONS OWNED BY EMPLOYER**

1. If the Contribution was written by the Contributor in the course of the Contributor's employment as a “work-made-for-hire” in the course of employment, the Contribution is owned by the company/employer which must sign this Agreement (in addition to the Contributor’s signature) in the space provided below. In such case, the company/employer hereby assigns to Wiley-Blackwell, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in paragraph A above.

2. In addition to the rights specified as retained in paragraph B above and the rights granted back to the Contributor pursuant to paragraph C above, Wiley-Blackwell hereby grants back, without charge, to such company/employer, its subsidiaries and divisions, the right to make copies of and distribute the final published Contribution internally in print format or electronically on the Company’s internal network. Copies so used may not be resold or distributed externally. However, the company/employer may include information and text from the Contribution as part of an information package included with software or other products offered for sale or license or included in patent applications. Posting of the final published Contribution by the institution on a public access website may only be done with Wiley-Blackwell’s written permission, and payment of any applicable fee(s). Also, upon payment of Wiley-Blackwell’s reprint fee, the institution may distribute print copies of the published Contribution externally.

**E. GOVERNMENT CONTRACTS**

In the case of a Contribution prepared under U.S. Government contract or grant, the U.S. Government may reproduce, without charge, all or portions of any applicable fee(s). Also, upon payment of Wiley-Blackwell’s reprint fee, other products offered for sale or license or included in patent applications. Posting of the final published Contribution by the institution on a public access website may only be done with Wiley-Blackwell’s written permission, and payment of any applicable fee(s). Also, upon payment of Wiley-Blackwell’s reprint fee, the institution may distribute print copies of the published Contribution externally.

**F. COPYRIGHT NOTICE**

The Contributor and the company/employer agree that any and all copies of the final published version of the Contribution or any part thereof distributed or posted by them in print or electronic format as permitted herein will include the notice of copyright as stipulated in the Journal and a full citation to the Journal as published by Wiley-Blackwell.

**G. CONTRIBUTOR’S REPRESENTATIONS**

The Contributor represents that the Contribution is the Contributor’s original work, all individuals identified as Contributors actually contributed to the Contribution, and all individuals who contributed are included. If the Contribution was prepared jointly, the Contributor agrees to inform the co-Contributors of the terms of this Agreement and to obtain their signature to this Agreement or their written permission to sign on their behalf. The Contribution is submitted only to this Journal and has not been published before. (If excerpts from copyrighted works owned by third parties are included, the Contributor will obtain written permission from the copyright owners for all uses as set forth in Wiley-Blackwell’s permissions form or in the Journal’s Instructions for Contributors, and show credit to the sources in the Contribution.) The Contributor also warrants that the Contribution contains no libelous or unlawful statements, does not infringe upon the rights (including without limitation the copyright, patent or trademark rights) or the privacy of others, or contain material or instructions that might cause harm or injury.

**CHECK ONE BOX:**

[ ] Contributor-owned work

ATTACH ADDITIONAL SIGNATURE PAGES AS NECESSARY

[ ] Company/Institution-owned work

(made-for-hire in the course of employment)

[ ] U.S. Government work

Note to U.S. Government Employees

A contribution prepared by a U.S. federal government employee as part of the employee’s official duties, or which is an official U.S. Government publication, is called a “U.S. Government work,” and is in the public domain in the United States. In such case, the employee may cross out Paragraph A.1 but must sign (in the Contributor’s signature line) and return this Agreement. If the Contribution was not prepared as part of the employee’s duties or is not an official U.S. Government publication, it is not a U.S. Government work.

[ ] U.K. Government work

(Crown Copyright)

Note to U.K. Government Employees

The rights in a Contribution prepared by an employee of a U.K. government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown. U.K. government authors should submit a signed declaration form together with this Agreement. The form can be obtained via http://www.opsi.gov.uk/advice/crown-copyright/copyright-guidance/publication-of-articles-written-by-ministers-and-civil-servants.htm

[ ] Other Government work

Note to Non-U.S., Non-U.K. Government Employees

If your status as a government employee legally prevents you from signing this Agreement, please contact the editorial office.

[ ] NIH Grantees

Note to NIH Grantees

Pursuant to NIH mandate, Wiley-Blackwell will post the accepted version of Contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, see www.wiley.com/go/nihmandate.
To: Mrs. Samara Kuehne
Company:
Phone: 818-908-0287
Fax: 781-388-0507

From:
Date:
Pages including this cover page:

Message:

Re
Please complete this form even if you are not ordering reprints. This form MUST be returned with your corrected proofs and original manuscript. Your reprints will be shipped approximately 4 weeks after publication. Reprints ordered after printing are substantially more expensive.

**REPRINT BILLING DEPARTMENT • 111 RIVER STREET, HOBOKEN, NJ 07030**

**PHONE: (201) 748-8789; FAX: (201) 748-6052**

**E-MAIL: reprints @ wiley.com**

**PREPUBLICATION REPRINT ORDER FORM**

Please complete this form even if you are not ordering reprints. This form MUST be returned with your corrected proofs and original manuscript. Your reprints will be shipped approximately 4 weeks after publication. Reprints ordered after printing are substantially more expensive.

**JOURNAL: Dialysis & Transplantation**

**TITLE OF MANUSCRIPT**

**MS. NO.**

**NO. OF PAGES**

**AUTHOR(S)**

---

**REPRINTS 8 1/4 X 11**

<table>
<thead>
<tr>
<th>No. of Pages</th>
<th>100 Reprints</th>
<th>200 Reprints</th>
<th>300 Reprints</th>
<th>400 Reprints</th>
<th>500 Reprints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>$636</td>
<td>$501</td>
<td>$694</td>
<td>$890</td>
<td>$1,052</td>
</tr>
<tr>
<td>5-8</td>
<td>$469</td>
<td>$703</td>
<td>$987</td>
<td>$1,251</td>
<td>$1,477</td>
</tr>
<tr>
<td>9-12</td>
<td>$594</td>
<td>$923</td>
<td>$1,234</td>
<td>$1,565</td>
<td>$1,850</td>
</tr>
<tr>
<td>13-16</td>
<td>$714</td>
<td>$1,156</td>
<td>$1,527</td>
<td>$1,901</td>
<td>$2,273</td>
</tr>
<tr>
<td>17-20</td>
<td>$794</td>
<td>$1,340</td>
<td>$1,775</td>
<td>$2,212</td>
<td>$2,648</td>
</tr>
<tr>
<td>21-24</td>
<td>$914</td>
<td>$1,529</td>
<td>$2,031</td>
<td>$2,536</td>
<td>$3,037</td>
</tr>
<tr>
<td>25-28</td>
<td>$1,004</td>
<td>$1,707</td>
<td>$2,267</td>
<td>$2,828</td>
<td>$3,388</td>
</tr>
<tr>
<td>29-32</td>
<td>$1,108</td>
<td>$1,894</td>
<td>$2,515</td>
<td>$3,135</td>
<td>$3,755</td>
</tr>
<tr>
<td>33-36</td>
<td>$1,219</td>
<td>$2,092</td>
<td>$2,773</td>
<td>$3,456</td>
<td>$4,143</td>
</tr>
<tr>
<td>37-40</td>
<td>$1,329</td>
<td>$2,290</td>
<td>$3,033</td>
<td>$3,776</td>
<td>$4,528</td>
</tr>
</tbody>
</table>

**Covers**

| 100 Covers | $890 | 200 Covers | $145 | 300 Covers | $200 | 400 Covers | $255 | 500 Covers | $325 | Additional 100s | $65 |

Please send me __________ reprints of the above article at....................... $____________

Please send me __________ Generic covers of the above journal at....................... $____________

Please add appropriate State and Local Tax {Tax Exempt No.__________________} $____________

Please add 5% Postage and Handling.............................................................. $____________

**TOTAL AMOUNT OF ORDER**.............................................................. $____________

Please check one: 

- [ ] Check enclosed
- [ ] Bill me
- [ ] Credit Card

Credit Card No._____________________________ Signature____________________________ Exp. Date___________

Bill To:

Name ____________________________

Address/Institution ____________________________

______________________________

Purchase Order No. ____________________________

Ship To:

Name ____________________________

Address/Institution ____________________________

______________________________

Phone ____________________________

Fax ____________________________

E-mail: ____________________________

**REPRINTS ARE ONLY AVAILABLE IN lots OF 100. IF YOU WISH TO ORDER MORE THAN 500 REPRINTS, PLEASE CONTACT OUR REPRINTS DEPARTMENT AT (201)748-8659 FOR A PRICE QUOTE.**

John Wiley & Sons, Inc.
Publishers Since 1807

**PREPUBLICATION REPRINT ORDER FORM**

**Please complete this form even if you are not ordering reprints.**

This form MUST be returned with your corrected proofs and original manuscript. Your reprints will be shipped approximately 4 weeks after publication. Reprints ordered after printing are substantially more expensive.

**JOURNAL: Dialysis & Transplantation**

**TITLE OF MANUSCRIPT**

**MS. NO.**

**NO. OF PAGES**

**AUTHOR(S)**

---

**REPRINTS 8 1/4 X 11**

<table>
<thead>
<tr>
<th>No. of Pages</th>
<th>100 Reprints</th>
<th>200 Reprints</th>
<th>300 Reprints</th>
<th>400 Reprints</th>
<th>500 Reprints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>$636</td>
<td>$501</td>
<td>$694</td>
<td>$890</td>
<td>$1,052</td>
</tr>
<tr>
<td>5-8</td>
<td>$469</td>
<td>$703</td>
<td>$987</td>
<td>$1,251</td>
<td>$1,477</td>
</tr>
<tr>
<td>9-12</td>
<td>$594</td>
<td>$923</td>
<td>$1,234</td>
<td>$1,565</td>
<td>$1,850</td>
</tr>
<tr>
<td>13-16</td>
<td>$714</td>
<td>$1,156</td>
<td>$1,527</td>
<td>$1,901</td>
<td>$2,273</td>
</tr>
<tr>
<td>17-20</td>
<td>$794</td>
<td>$1,340</td>
<td>$1,775</td>
<td>$2,212</td>
<td>$2,648</td>
</tr>
<tr>
<td>21-24</td>
<td>$914</td>
<td>$1,529</td>
<td>$2,031</td>
<td>$2,536</td>
<td>$3,037</td>
</tr>
<tr>
<td>25-28</td>
<td>$1,004</td>
<td>$1,707</td>
<td>$2,267</td>
<td>$2,828</td>
<td>$3,388</td>
</tr>
<tr>
<td>29-32</td>
<td>$1,108</td>
<td>$1,894</td>
<td>$2,515</td>
<td>$3,135</td>
<td>$3,755</td>
</tr>
<tr>
<td>33-36</td>
<td>$1,219</td>
<td>$2,092</td>
<td>$2,773</td>
<td>$3,456</td>
<td>$4,143</td>
</tr>
<tr>
<td>37-40</td>
<td>$1,329</td>
<td>$2,290</td>
<td>$3,033</td>
<td>$3,776</td>
<td>$4,528</td>
</tr>
</tbody>
</table>

**Covers**

| 100 Covers | $890 | 200 Covers | $145 | 300 Covers | $200 | 400 Covers | $255 | 500 Covers | $325 | Additional 100s | $65 |

Please send me __________ reprints of the above article at....................... $____________

Please send me __________ Generic covers of the above journal at....................... $____________

Please add appropriate State and Local Tax {Tax Exempt No.__________________} $____________

Please add 5% Postage and Handling.............................................................. $____________

**TOTAL AMOUNT OF ORDER**.............................................................. $____________

Please check one: 

- [ ] Check enclosed
- [ ] Bill me
- [ ] Credit Card

Credit Card No._____________________________ Signature____________________________ Exp. Date___________

Bill To:

Name ____________________________

Address/Institution ____________________________

______________________________

Purchase Order No. ____________________________

Ship To:

Name ____________________________

Address/Institution ____________________________

______________________________

Phone ____________________________

Fax ____________________________

E-mail: ____________________________

**REPRINTS ARE ONLY AVAILABLE IN lots OF 100. IF YOU WISH TO ORDER MORE THAN 500 REPRINTS, PLEASE CONTACT OUR REPRINTS DEPARTMENT AT (201)748-8659 FOR A PRICE QUOTE.**
Acrobat annotation tools can be very useful for indicating changes to the PDF proof of your article. By using Acrobat annotation tools, a full digital pathway can be maintained for your page proofs.

The NOTES annotation tool can be used with either Adobe Acrobat 4.0, 5.0 or 6.0. Other annotation tools are also available in Acrobat 4.0, but this instruction sheet will concentrate on how to use the NOTES tool. Acrobat Reader, the free Internet download software from Adobe, DOES NOT contain the NOTES tool. In order to softproof using the NOTES tool you must have the full software suite Adobe Acrobat 4.0, 5.0 or 6.0 installed on your computer.

Steps for Softproofing using Adobe Acrobat NOTES tool:

1. Open the PDF page proof of your article using either Adobe Acrobat 4.0, 5.0 or 6.0. Proof your article on-screen or print a copy for markup of changes.

2. Go to File/Preferences/Annotations (in Acrobat 4.0) or Document/Add a Comment (in Acrobat 6.0 and enter your name into the “default user” or “author” field. Also, set the font size at 9 or 10 point.

3. When you have decided on the corrections to your article, select the NOTES tool from the Acrobat toolbox and click in the margin next to the text to be changed.

4. Enter your corrections into the NOTES text box window. Be sure to clearly indicate where the correction is to be placed and what text it will effect. If necessary to avoid confusion, you can use your TEXT SELECTION tool to copy the text to be corrected and paste it into the NOTES text box window. At this point, you can type the corrections directly into the NOTES text box window. **DO NOT correct the text by typing directly on the PDF page.**

5. Go through your entire article using the NOTES tool as described in Step 4.

6. When you have completed the corrections to your article, go to File/Export/Annotations (in Acrobat 4.0) or Document/Add a Comment (in Acrobat 6.0).

7. **When closing your article PDF be sure NOT to save changes to original file.**

8. To make changes to a NOTES file you have exported, simply re-open the original PDF proof file, go to File/Import/Notes and import the NOTES file you saved. Make changes and re-export NOTES file keeping the same file name.

9. When complete, attach your NOTES file to a reply e-mail message. Be sure to include your name, the date, and the title of the journal your article will be printed in.