temic sclerosis and anti-Jo1 in polymyositis, and exceeds that of anti-Sm in systemic lupus erythematosus.[6]

Wolfgang Hassfeld, M.D.
A-1130 Vienna, Austria Lainz Hospital

Günter Steiner, Ph.D.
A-1090 Vienna, Austria University of Vienna

Josef S. Smolen, M.D.
A-1130 Vienna, Austria Lainz Hospital

1. Nienhuis RLF, Mandema E, Smids C. A new serum factor in patients with rheumatoid arthritis: the antiperinuclear factor. Ann Rheum Dis 1964; 23:302-5.
2. Tan EM. The LE cell and antinuclear antibodies: a breakthrough in diagnosis. In: McCarty DJ, ed. Landmark advances in rheumatology. Atlanta: Contact Associates, 1985:43-52.
3. Alspaugh MA, Jensen FC, Rabin H, Tan EM. Lymphocytes transformed by Epstein–Barr virus: induction of nuclear antigen reactive with antibody in rheumatoid arthritis. J Exp Med 1978; 147:1018-27.
4. Hassfeld W, Steiner G, Hartmuth K, et al. Demonstration of a new antinuclear antibody (anti-RA33) that is highly specific for rheumatoid arthritis. Arthritis Rheum 1989; 32:1515-20.
5. Reichlin M, Harley JB. ANA subsets in systemic lupus erythamatosus. In: Smolen JS, Zielinski CC, eds. Systemic lupus erythematosus: clinical and experimental aspects. Berlin: Springer-Verlag, 1987:105-23.
6. Van Venrooij WJ, Sillekens PT. Small nuclear RNA associated proteins: autoantigens in connective tissue diseases. Clin Exp Rheumatol 1989; 7:635-45.

To the Editor: The review article by Dr. Harris on the pathophysiology and therapy of rheumatoid arthritis is very informative. However, two corrections need to be pointed out. In the section discussing the sharing of epitopes between Epstein–Barr virus glycoprotein gp110 and the Dw4 subtype of HLA-DR4, the correct sequence of the shared epitope is glutamic acid-glutamine-lysine-arginine-alanine-alanine (i.e., Glu-Gln-Lys-Arg-Ala-Ala).[1] Moreover, the amino acid sequence for positions 70 through 74 on HLA-DR1 and the Dw14 subtype of HLA-DR4 is Gln-Arg-Arg-Ala-Ala, and for the Dw4 subtype of HLA-DR4 it is Gln-Lys-Arg-Ala-Ala.[2]

Muhammad Asim Khan, M.D.
Cleveland, OH 44109 MetroHealth Medical Center

1. Vaughan JH. Infection and rheumatic diseases: a review. Bull Rheum Dis 1990; 39:1-8.
2. Wordsworth BP, Lanchbury JS, Sakkas LI, Welsh KI, Panayi GS, Bell JI. HLA-DR4 subtype frequencies in rheumatoid arthritis indicate that DRB1 is the major susceptibility locus within the HLA class II region. Proc Natl Acad Sci U S A 1989; 86:10049-53.

To the Editor: Having treated patients with rheumatoid arthritis for more than 30 years and followed many for up to 23 years, we agree with Harris that rest of a joint is the basic therapy, since the fundamental disturbance in the physiology of the rheumatoid joint is ischemia and reperfusion injury. But contrary to Harris' opinion, combinations of currently available agents have kept the vast majority of our patients on the job, with acceptable levels of toxicity. When first seen by us, nearly all of these patients had erosive disease, which would be classified by Harris as "stage 5" — untreatable except by physical therapy, occupational therapy, and reconstructive joint surgery. Progressive destruction of joints with radiologic erosions is not inevitable and in some instances is reversible. We do share his dim view of current empirical therapy for rheumatoid arthritis. Like Harris, we would of course welcome more specific therapeutic methods.

Serial reproducible measurements reflecting the severity of joint inflammation should be obtained at each patient visit so that the therapist can determine whether or not inflammation is adequately controlled. Unfortunately, most rheumatologists fail to do this routinely. Such measurements are the key to successful therapy with currently available agents. Once remission is obtained, and this is achievable in the majority of cases, the medication must not be stopped since the disease will almost always recur.

In summary, we agree with Dr. Harris that less toxic agents are needed, but until that time a rational application of available drugs singly or in combination if necessary will usually be adequate for satisfactory control of rheumatoid arthritis, even in patients with relatively advanced joint damage.

Daniel J. McCarty, M.D.
Geraldine M. McCarthy, M.D.
Milwaukee, WI 53226 Medical College of Wisconsin

The above letters were referred to Dr. Harris, who offers the following reply:

To the Editor: The short review of Pincus and Callahan makes many interesting points. There is no doubt that our current assays of articular structure in rheumatoid arthritis are poor; we lack the capability of appreciating the state of the cartilage. Magnetic resonance imaging may be the best imaging technique, but it is too expensive for routine use. Radiographic severity is associated with the HLA-DR4 haplotype; indeed, it is the subgroup of patients with this haplotype who deserve more aggressive, early therapy. I disagree with the implication of Pincus and Callahan that we should be empirical in therapy to the exclusion of trying to figure out the pathologic phase of disease. It is only by synthesizing the data available into a picture of disease activity and rate of progression that we will know which patient to treat, when to treat, and which drug to use. For example, I recently cared for a patient who had been treated to the point of severe toxicity with methotrexate and azathioprine; she had joint pain and a positive rheumatoid factor, but no evidence of proliferative synovitis or loss of cartilage. It is unlikely that her condition would ever progress to seriously erosive disease, and she should not have been treated as if it would.

Dr. Hassfeld and his colleagues focus our attention on a new antibody (anti-RA33) with a high degree of specificity but a rather low sensitivity. In time, large population studies will be essential for us to learn whether the presence of this antibody can better our clinical assessment in making the diagnosis of rheumatoid arthritis.

The letter from Dr. Kahn is useful. Looking at "susceptibility cassettes" is important in that HLA-DR1 and DRw4 confer the same increased relative risk of rheumatoid arthritis, yet other DR subtypes, with small differences in amino acid sequences in positions 70 through 74 (e.g., HLA-Dw2), have no positive (and perhaps some negative) association with the disease.

The aggressive early therapy of McCarty and McCarthy is, in their hands, effective. It is crucial that patients be subclassified into groups based on DR–β-chain sequencing so that those with the susceptibility cassette are the ones randomly assigned to special therapy. It is important that toxic drugs not be given to patients with rheumatoid arthritis that is not destined to become severe. Finally, it is a fact that destruction of articular cartilage is irreversible. Erosions of bone may heal, but once lost, cartilage is gone forever.

Edward D. Harris, Jr., M.D.
Stanford, CA 94305 Stanford University School of Medicine

AEROSOLIZED AMILORIDE FOR THE TREATMENT OF LUNG DISEASE IN CYSTIC FIBROSIS

To the Editor: The April 26 issue of the *Journal* presented encouraging results by Knowles et al. regarding the beneficial effects of aerosolized amiloride in the treatment of cystic fibrosis.[1] The introduction and discussion sections of this article described the function of amiloride as an inhibitor of sodium transport in the airway epithelium, and the authors suggested that the beneficial effects observed were exerted "at least in part by increasing the clearance of secretions." Although the results of this investigation were promising in terms of the improvement in the decline of forced vital capacity in patients with cystic fibrosis, this discussion of the mechanism of amiloride's beneficial effect is misleading.

The cellular effects of amiloride have been the subject of numerous investigations that have demonstrated clearly that this drug's range of activity exceeds that of a specific inhibitor of the sodium channel, as was suggested by Knowles et al. As an inhibitor of ion transport, amiloride has activity in a variety of cell types at sites of sodium–hydrogen and sodium–calcium exchange,[2] in addition to the selective inhibition of calcium channels.[3] The action of amiloride at the level of hydrogen transport has been correlated with its potent ability to inhibit neutrophil activation in vitro.[4] Furthermore, amiloride has been demonstrated to inhibit directly protein synthesis[5] and the activity of DNA topoisomerase.[6]

An alternative explanation for the observed effect of amiloride in patients with cystic fibrosis may lie in its activity as a potent anti-inflammatory agent. Studies in our laboratory have shown that amiloride inhibits cutaneous inflammation induced in mice by exposure to contact allergens or ultraviolet radiation.[7] Additional unpublished studies in our laboratory have also shown the inhibition of interleukin-3 and the release of granulocyte–macrophage colony-stimulating factor from keratinocytes in vitro that were exposed to amiloride for 30 minutes. Interestingly, this effect occurred at doses similar to those delivered to the airways of patients with cystic fibrosis (0.5 mM).

Current evidence suggests, therefore, that multiple cellular mechanisms may be influenced by the aerosolized delivery of amiloride to patients with cystic fibrosis. Knowles et al. point out in their article that the mechanism of action of amiloride on the airway epithelium of patients with cystic fibrosis is uncertain. Given the range of alternative explanations for the observed beneficial activity of this drug, it would be useful to evaluate and discuss these possibilities in future studies.

Richard L. Gallo, M.D., Ph.D.
Massachusetts General Hospital
Boston, MA 02114

1. Knowles MR, Church NL, Waltner WE, et al. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med 1990; 322:1189-94.
2. Benos DJ. Amiloride: a molecular probe of sodium transport in tissues and cells. Am J Physiol 1982; 242:C131-C145.
3. Tang C-M, Presser F, Morad M. Amiloride selectively blocks the low threshold (T) calcium channel. Science 1988; 240:213-5.
4. Berkow RL, Dodson RW, Kraft AS. Dissociation of human neutrophil activation events by prolonged treatment with amiloride. J Lab Clin Med 1987; 110:97-105.
5. Lubin M, Cahn F, Coutermarsh BA. Amiloride, protein synthesis, and activation of quiescent cells. J Cell Physiol 1982; 113:247-51.
6. Besterman JM, Elwell LP, Blanchard SG, Cory M. Amiloride intercalates into DNA and inhibits DNA topoisomerase II. J Biol Chem 1987; 262:13352-8.
7. Gallo RL, Granstein RD. Inhibition of allergic contact dermatitis and ultraviolet radiation-induced tissue swelling in the mouse by topical amiloride. Arch Dermatol 1989; 125:502-6.

To the Editor: Knowles et al. describe a promising new therapeutic approach to the treatment of cystic fibrosis using aerosolized amiloride, a sodium-channel blocker. They concluded that this compound can be administered safely to adults with cystic fibrosis on the basis of studies in 14 patients who completed the study. However, a little-known property of amiloride, inhibition of the plasminogen activator urokinase, should be a reason for caution in future expanded trials, especially in view of the newly appreciated role of urokinase plasminogen activator in pulmonary function.

Vassalli and Belin[1] reported that amiloride inhibits urokinase with an inhibition constant (K_i) of 7 μM, and we have confirmed this result. The aerosol used in the study of Knowles et al. contained more than 700 times this concentration and, even if substantially diluted with lung fluids, would be expected to lead to more than 95 percent inhibition of alveolar urokinase. Alveolar macrophages and probably alveolar epithelial cells synthesize urokinase,[2] and depressed urokinase activity partly attributed to an excess of plasminogen-activator inhibitor has been observed in the adult respiratory distress syndrome.[3] Deposition of fibrin in distal air spaces is thought to have a role in both acute and chronic lung disorders, and if fibrin deposition is prolonged, fibrosis may result from collagen deposition and scarring over the fibrin strands.[4] Alveolar urokinase and plasminogen probably have a role in keeping the lung free of fibrin and also in rapidly clearing hemorrhage into the lung.[2] These enzymes are also implicated in lung-matrix metabolism.[5] Thus, there are at least theoretical conditions in which strong inhibition of urokinase by amiloride may be harmful, and more extensive studies will be required before this aerosol can be considered totally safe.

Jack Henkin, Ph.D.
Abbott Laboratories
Abbott Park, IL 60064

1. Vassalli JD, Belin D. Amiloride selectively inhibits the urokinase-type plasminogen activator. FEBS Lett 1987; 214:187-91.
2. Chapman HA JR, Bertozzi P, Reilly JJ Jr. Role of enzymes mediating thrombosis and thrombolysis in lung disease. Chest 1988; 93:1256-63.
3. Bertozzi P, Astedt B, Zenzius L, et al. Depressed bronchoalveolar urokinase activity in patients with adult respiratory distress syndrome. N Engl J Med 1990; 322:890-7.
4. McDonald JA. The yin and yang of fibrin in the airways. N Engl J Med 1990; 322:929-31.
5. Chapman HA Jr, Reilly JJ Jr, Kobzik L. Role of plasminogen activator in degradation of extracellular matrix protein by live human alveolar macrophages. Am Rev Respir Dis 1988; 137:412-9.

The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: With reference to Dr. Gallo's comments about amiloride's mode of action, we had not discounted mechanisms other than the inhibition of sodium transport as perhaps playing a part in the beneficial effect. Hence, we commented that amiloride probably exerts a beneficial effect "at least in part" through its demonstrated effect on the abnormal sodium transport in airway epithelia in cystic fibrosis[1]; space limitations precluded a full discussion of other possible effects. We recognize that amiloride can affect multiple cellular functions and that some of these effects might be pertinent to its beneficial action in the airways of patients with cystic fibrosis. However, substantial alteration in cell function other than transepithelial electrogenic sodium transport usually requires a dose 1 to 2 logs higher[2,3] than even the peak concentration of amiloride (0.08 mM) achieved on conducting airway surfaces of patients with cystic fibrosis by aerosol delivery. The effect of amiloride to inhibit induced cutaneous inflammation in mice is intriguing, but it should be noted that this antiinflammatory effect occurred at drug concentrations at least 1 log higher than the peak concentration of 0.08 mM on conducting airway surfaces.

Dr. Henkin's caution that further studies of safety are required is in accordance with our view of this pilot study. Amiloride is known to inhibit trypsin-like proteases[4,5] — an effect that may be beneficial in limiting proteolytic activity associated with chronic bacterial infection and suppuration in the conducting airways of patients with cystic fibrosis.[6,7] Strong inhibition of the plasminogen activator urokinase in alveolar regions could theoretically be harmful, but available information would suggest that is an unlikely result of treatment with aerosolized amiloride in patients with cystic fibrosis. Cystic fibrosis is a disease of the conducting airways, and the aerosolized formulation of inhaled amiloride is targeted to airways rather than alveolar regions, which have a surface area 20 times greater than that of the conducting airways. After delivery of the aerosol, the alveolar surfaces probably have a concentration of amiloride 1 to 2 logs lower than that of the conducting airways, and the alveolar concentration of amiloride would have little inhibitory effect on urokinase. Safety studies performed to date are in accordance with this prediction. In addition to the pilot study in patients with cystic fibrosis, we observed no change in pulmonary function or gas-exchange indexes in normal human volunteers after a one-month exposure to aerosolized amiloride four times daily.[8] We also saw no pulmonary function or histologic changes in hamster lungs after three months' exposure to aerosolized amiloride generated by ultrasonic nebulization (unpublished data filed with the Food and Drug Administration). A placebo-controlled multicenter study of aerosolized amiloride is expected to be initiated in 100 to 120 patients with cystic fibrosis in the near future. Its design will incorporate key

aspects of the pilot study and include measures that will attempt to address further the safety of aerosolized amiloride and the mechanisms of any beneficial effects.

Michael R. Knowles, M.D., Nina L. Church, M.S., William E. Waltner, M.D., James R. Yankaskas, M.D., and Peter Gilligan, Ph.D.
Chapel Hill, NC 27599 University of North Carolina

Malcolm King, Ph.D.
Edmonton, AB T6G 2G3, Canada University of Alberta

Lloyd J. Edwards, M.S.
Ronald W. Helms, Ph.D.
Richard C. Boucher, M.D.
Chapel Hill, NC 27599 University of North Carolina

1. Boucher RC, Stutts MJ, Knowles MR, Cantley L, Gatzy JT. Na+ transport in cystic fibrosis respiratory epithelia: abnormal basal rate and response to adenylate cyclase activation. J Clin Invest 1986; 78:1245-52.
2. Benos DJ. Amiloride: a molecular probe of sodium transport in tissues and cells. Am J Physiol 1982; 242:C131-C145.
3. Kleyman TR, Cragoe EJ Jr. Amiloride and its analogs as tools in the study of ion transport. J Membr Biol 1988; 105:1-21.
4. Margolius HS, Chao J. Amiloride inhibits mammalian renal kallikrein and a kallikrein-like enzyme from toad bladder and skin. J Clin Invest 1980; 65:1343-50.
5. Vassalli J-D, Belin D. Amiloride selectively inhibits the urokinase-type plasminogen activator. FEBS Lett 1987; 214:187-91.
6. Bruce MC, Poncz L, Klinger JD, Stern RC, Tomashefski JF Jr, Dearborn DG. Biochemical and pathologic evidence for proteolytic destruction of lung connective tissue in cystic fibrosis. Am Rev Respir Dis 1985; 132:529-35.
7. Goldstein W, Doring G. Lysosomal enzymes from polymorphonuclear leukocytes and proteinase inhibitors in patients with cystic fibrosis. Am Rev Respir Dis 1986; 134:49-56.
8. Waltner WE, Church NL, Gatzy JT, Boucher RC, Knowles MR. Deposition, pharmacokinetics, and toxicity of amiloride aerosol in normal and cystic fibrosis (CF) subjects. Am Rev Respir Dis 1987; 135:Suppl:A288. abstract.

TREATMENT OF PEPTIC ULCER

To the Editor: Dr. Soll's informative and well-written review article on the pathogenesis of peptic ulcer and implications for therapy (March 29 issue)* contains one rather grave omission.

In his discussion of refractory ulcers — meaning ulcers, ulcer symptoms, or both that do not heal after 12 weeks — Dr. Soll states that several treatment options are available but that none have been tested in controlled trials. Two time-tested treatment methods for those ulcers are elective vagotomy and antrectomy and elective proximal gastric vagotomy with or without pyloroplasty. With negligible mortality and very low morbidity, the patient can look forward to a symptom-free, ulcer-free, pill-free, doctor-free, and endoscopy-free future life. Either of these definitive treatments can bring patients back to their regular employment and be very cost effective as well.

I believe, therefore, that physicians should advise patients with refractory ulcers that among the various treatment methods available, surgery is certainly a reasonable choice. It is profoundly distressing to the surgeon when a patient, confronted with the need for emergency surgery for massive hemorrhage, perforation, or gastric-outlet obstruction due to a refractory ulcer, asks why the option of surgery was never presented before disaster occurred.

Hans H.C. Morsch, M.D.
Mount Kisco, NY 10549 666 Lexington Ave.

*Soll AH. Pathogenesis of peptic ulcer and implications for therapy. N Engl J Med 1990; 322:909-16.

To the Editor: In his excellent review, Dr. Soll claims that there is probably no difference between the treatment of gastric and that of duodenal ulcers. He states, however, that gastric ulcers, except the prepyloric ones, are less dependent on acid secretion than duodenal ulcers. This arouses some concern about whether powerful antisecretory drugs are the best therapeutic choice in ulcers that occur proximally in the stomach. It is true, on the other hand, that many clinical trials have shown the benefit of controlling acid secretion in gastric ulcers.[1] However, the high rates of healing reported in most of these trials are calculated by considering antral and body ulcers together. Consequently, the good response to powerful antisecretory compounds could depend mainly on the frequent predominance of antral over body ulcers, because the former behave like typical duodenal ulcers. For example, in a recent U.S. trial,[2] famotidine provided significantly higher rates of healing than placebo in treating gastric ulcers, but this superiority was evident only for antral ulcers, which represented more than 70 percent of the ulcers studied. Thus, one should be cautious in extending the benefit of antisecretory treatment to the entire group of gastric ulcers.

In addition, the use of omeprazole, the most powerful acid-suppressant agent, has led to conflicting results in comparisons with H_2-receptor antagonists in the treatment of proximal gastric ulcers,[3-5] probably because it provides only a partial correction of the major pathophysiologic alterations in this disease.[6] Finally, using a technique that allows continuous time-dependent intragastric pH measurements,[7] we found that the circadian acidity of proximal gastric ulcers is remarkably lower than that of duodenal ulcers,[8,9] with a particularly striking difference during the night. In view of this, the treatment of proximal gastric ulcers with potent acid inhibitors and the usual bedtime dosing of H_2 antagonists seem to lack strong physiologic support.

These considerations seem to undermine the rationale not only of using antisecretory drugs but also of prescribing the same doses and administration times of these compounds for all kinds of peptic ulcers, regardless of their location. Clinical trials that make clear-cut distinctions between body and antral gastric ulcers will be helpful in clarifying this problem.

Vincenzo Savarino, M.D.
Giuseppe Sandro Mela, M.D.
Guido Celle, M.D.
16132 Genoa, Italy Istituto Scientifico di Medicina Interna

1. Chiverton SG, Hunt RH. Medical regimens in short- and long-term ulcer management. Baillieres Clin Gastroenterol 1988; 2:655-76.
2. McCullough AJ, Graham DY, Knuff TE, et al. Suppression of nocturnal acid secretion with famotidine accelerates gastric ulcer healing. Gastroenterology 1989; 97:860-6.
3. Classen M, Dammann HG, Domschke W, et al. Abheilungsraten nach Omeprazol- und Ranitidin-Behandlung des Ulcus ventriculi: Ergebnisse einer deutschen Multizenterstudie. Dtsch Med Wochenschr 1985; 110:628-33.
4. Walan A, Bader J-P, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989; 320:69-75.
5. Danish Omeprazole Study Group. Omeprazole and cimetidine in the treatment of ulcers of the body of the stomach: a double blind comparative trial. BMJ 1989; 298:645-7.
6. Savarino V, Mela GS, Celle G. Omeprazole and cimetidine in treating ulcers of the body of the stomach. BMJ 1989; 298:1249-50.
7. Savarino V, Mela GS, Zentilin P, et al. Gastric aspiration versus antimony and glass pH electrodes: a simultaneous comparative in vivo study. Scand J Gastroenterol 1989; 24:434-9.
8. Savarino V, Mela GS, Scalabrini P, Sumberaz A, Fera G, Celle G. 24-hour study of intragastric acidity in duodenal ulcer patients and normal subjects using continuous intraluminal pH-metry. Dig Dis Sci 1988; 33:1077-80.
9. Savarino V, Mela GS, Zentilin P, Celle G. Ulcer heterogeneity: further arguments in favor of a range of antisecretory treatment. Dig Dis Sci (in press).

The above letters were referred to Dr. Soll, who offers the following reply:

To the Editor: Dr. Morsch's point is well taken; surgery remains an important option for ulcer disease, a topic not covered in my brief overview. Unfortunately, therapeutic decisions regarding current treatments, both medical and surgical, must be made without benefit of controlled trials, which sometimes yield different approaches from those reached by testing over time. In a healthy patient with a refractory ulcer, surgery is an attractive alternative. However, troublesome ulcers have a predilection for otherwise sick patients for