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Now for the "complexity issue," which I believe is Professor Emmett's major criticism of Stewart's theory. Just as Newtonian physics may be regarded as a subset of Einstein's relativity, the traditional model of acid-base balance may be thought of as a subset of Stewart's more general theory. Professor Emmett is correct in that both Newtonian physics and traditional acid-base theory are useful to describe commonly observed phenomenon. However, in actuality, light bends and so does the buffer curve. In the era of the palmtop computer, mathematical complexity should not impede progress either in physics or in physiology.

HOWARD E. COREY
Morristown, New Jersey

Correspondence to Morristown Memorial Hospital, Pediatric Nephrology Box 24, Morristown, NJ 07962.
E-mail: hcorey@airbridge.net

$CD28^-$ T cells display features of effector memory T cells in Wegener's granulomatosis

To the Editor: We read with interest the article by Vogt et al [1], who found shortening of telomers and reduced CD28 expression on T-cells in Wegener's granulomatosis (WG). Several groups have shown an expansion of circulating $CD8^+$ and $CD4^+$ T-cells lacking the costimulatory molecule CD28 in WG. The expansion of circulating $CD28^-$ T-cells is already evident in patients with initial disease manifestations and correlates with organ involvement [2]. $CD4^+CD28^-$ and $CD8^+CD28^-$ T-cells are enriched in broncho-alveolar lavage fluid. In granulomatous lesions of the respiratory tract in WG, T-cells completely lack CD28 expression. Circulating peripheral blood and granuloma $CD4^+CD28^-$ T-cells are a major source of Th1-type cytokine secretion [3]. The Th1-type chemokine receptor CCR5 is expressed on $CD28^-$ T-cells and may favor recruitment of $CD28^-$ T-cells into inflammatory lesions [2]. Of note, circulating $CD4^+CD28^-$ T-cells express the differentiation marker CD57 (HNK-1) and the activation marker CD18 (β_2-integrin). The expression of these cell surface markers and the restriction of Th1-type cytokine production to IFN-γ and TNF-α and perforin expression of $CD4^+CD28^-$ T-cells in WG is typical of so-called late differentiated or effector memory T-cells [3]. Shortening of telomer length as a sign of replicative senescence of T-cells is in line with the finding of an expanded subset of effector memory T-cells. $CD8^+CD28^-$ cells display heterogeneous CD27 expression, features which are also seen in antigen-specific (cytomegalovirus-) T-cells in WG, but not in controls, suggesting profound generalized changes in the $CD8^+$ T-cell compartment also affecting virus-specific T-cell responses in WG [4].

PETER LAMPRECHT, ANTJE MUELLER, and WOLFGANG L. GROSS
Luebeck, Germany

Correspondence to Peter Lamprecht, University Hospital of Schleswig-Holstein, Department of Rheumatology, Ratzeburger Allee 160, Luebeck 23538, Germany.
E-mail: lamprecht@rheuma-zentrum.de

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Reply from the Authors

We appreciate the comment and the reference to the publications—cited as [2] and [4]—which were not yet available when we were submitting our manuscript. Basically, we agree that there are small numbers of CD4+$CD28^-$ T-cells in patients with Wegener's granulomatosis (5.4% as cited by Lamprecht et al [1] and approximately 3% in our study). The more intriguing finding of our study, however, is that the majority of $CD28^-$ cells are $CD8^+$ T-cells. They amount to 60% in some patients (mean 45.2 ± 15.5, $N = 22$). Since submission of our manuscript, several publications dealing with the identification of $CD28^-$ T-cells have appeared, and there is now increasing evidence that these represent memory/effector cells [2, 3]. Following antigenic challenge, naive T-cells enter a program of differentiation and proliferation, and ultimately become memory cells. These cells do not have short telomeres; there is, however, evidence for increased division rates, as seen by reduced levels of T-cell receptor excision cycles [4]. It is reasonable to assume that during long-term, severe chronic inflammatory disease, as in Wegener's granulomatosis, these cells eventually reach their finite number of cell divisions and enter a state of senescence associated with shortening of the telomeres. This assumption is in accordance with the data derived from studies on persistent (virus) infection [3, 5].

Of note is that senescent T-cells do not express CD28, but that, on the other hand, not all $CD28^-$ T-cells are senescent.

GERTRUD MARIA HÄNSCH
and KONRAD ANDRASSY
Heidelberg, Germany

Correspondence to Maria Hänsch, Heidelberg University, Heidelberg, Germany.
E-mail: n50@ix.urz.uni-heidelberg.de

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The impact of antiretroviral therapy on HIVAN

To the Editor: We read with interest the article by Wei et al [1] on the association between anigotensin-converting enzyme inhibition (ACE-I) and outcomes among patients with human immunodeficiency virus–associated nephropathy (HIVAN). We are concerned about the inherent limitations in making concrete conclusions from observational data and would caution nephrologists against relying too heavily on ACEI, while de-emphasizing the role of antiretroviral therapy (ARV) in the treatment of HIVAN. The authors show that fosinopril, not ARV, is an important predictor of mortality. With the introduction of highly active antiretroviral therapy (HAART), the survival benefit from ARV therapy is indisputable. Failure to show such a benefit raises important questions about the data; specifically, what classes of ARV were available during the course of this study. In the absence of more information in this regard, it is conceivable that the benefits of ACE-I, which decreased the risk of death 100-fold, may be overstated.

The cohort was recruited between 1993–1997 before the availability of HAART, and the current work represents long-term follow-up of the original survivors. Only 16 patients were followed for more than one year, minimally overlapping the contemporary era in which HAART has so significantly improved survival. Most of these patients were treated with ACE-I and were originally coded as not taking ARV. Because most of the deaths occurred within the first year of enrollment, it would not be fair to ascribe long-term benefits of survivors to ACE-I if, in fact, survivors had access to potent ARV, such as HAART, years after they were coded as not having been treated at baseline. Another concern is the observation that the cohort includes 11 patients who survived but were followed for less than one year. All 11 of these patients were taking ARV. Said another way, survivors not taking ARV were followed for 1200 days, while survivors taking ARV were followed for only 385 days. There seems to be considerable nonrandom loss to follow-up in the ARV group, which by itself would skew the data to more favorable outcomes for ACE-I. Bias could also be introduced by factors not included in this analysis, such as perceptions about patient compliance, which could influence the decision to begin antiretroviral therapy or ACE-I, HIV RNA levels, and how CD4 count and HIV RNA levels change over time with ARV. Finally, nonrandom misclassification bias likely impacted the significance of ARV on outcomes. The definition of ARV exposure is $\geq$30 consecutive days. This is not sufficient exposure to derive any meaningful benefit from the drugs, yet patients with minimal exposure could easily have been labeled as having been treated.

Therefore, for these reasons, we do not believe these data can assess the impact of ARV on renal outcomes among patients with HIVAN. Given prior reports which suggest that increasing CD4 lymphocyte counts and nondetectable HIV RNA levels are associated with better renal outcomes [2, 3], and the trend toward greater use of antiretroviral medications in the group receiving fosinopril, we believe that the *real* question not addressed by these data becomes "Does disrupting the renin-angiotensin system affect the progression of HIVAN among patients with effective suppression of viral replication?"

LYNDA ANNE SZCZECH
and JONATHAN A. WINSTON
Durham, North Carolina,
and New York, New York

Correspondence to Lynda Anne Szczech, Duke University Medical Center, Box 3646, Durham, NC 27710.
E-mail: sczcze001@mc.duke.edu

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