isoform recognized by the N-terminal antibody in patient samples is presumably encoded by a different transcript. Thus, the calcineurin signaling pathway predominating in normal tissue may in fact be compromised rather than induced in the failing human heart.

These experiments raise several intriguing issues. The levels of calmodulin-associated calcineurin in a cell may not be as informative as the identification of the particular isoform in these complexes. Moreover, whereas calcineurin levels are generally increased in skeletal myocyte hypertrophy, those calcineurin complexes associated with fully dephosphorylated substrates and localized to the nucleus did not contain calmodulin[4]. If the same holds true for cardiac muscle, new assays are needed to accurately assess active calcineurin levels, either in hypertrophic or in failed heart tissue.

The differential regulation of distinct calcineurin isoforms in failing heart tissue demonstrates an unexpectedly complex role for the calcineurin pathway. Calcineurin isoform shifts during human cardiac dilatation may underlie the maladaptive response to myocardial injury, consistent with the rapid decompensation seen in mice expressing constitutively activated calcineurin transgenes in the myocardium[1]. Alternatively, myocardial damage may prompt production of a constitutively activated calcineurin isoform as a final but futile compensatory measure. Further investigation is needed to evaluate particular calcineurin isoforms as a cause or consequence of heart failure.

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Lim and Molkentin reply—We previously identified a significant increase in the content of calcineurin protein associated with calmodulin in failed human hearts, indicative of activation[3]. These data are consistent with a recent report in which calcineurin protein content was found to be increased in dilated cardiomyopathy in humans[5]. Since that report, we have invested considerable effort in dissecting the regulation of the three calcineurin catalytic genes in hypertrophied and failed heart. We have determined that both the CnA-α and CnA-β genes are expressed in the heart and that CnA-β, but not CnA-α, mRNA and protein are upregulated approximately 300% by hypertrophic agonist in cultured cardiomyocytes, and that enzymatic activity is increased to a similar extent[6]. *In vivo*, we have found that calcineurin protein content and catalytic activity are significantly increased in pressure-loaded rat hearts[7]. We have also re-evaluated calcineurin activation in failed human hearts using an enzymatic phosphatase assay. In eight control human left ventricular heart samples, calcineurin enzymatic activity was 100% ± 7%, compared with 171% ± 11% in twelve failed hearts (P = 0.007). This 71% increase in calcineurin enzymatic activity indicates that calcineurin activation is associated with human heart failure.

This increase in calcineurin enzymatic activity in failed human hearts is partially consistent with the results of Tsao *et al*. (Fig. 1*a*), in that failed hearts show an increase in calcineurin protein corresponding to the catalytic domain, which is potentially constitutively active (lacking the regulatory domain). However, it is likely that calcineurin is subject to multiple levels of regulation in diseased myocardium. Indeed, at least three alternative splicing events have been described in the C terminus (regulatory domain) of CnA-α and CnA-β (ref. 8). Collectively, these results emphasize the complexity of calcineurin regulation in the heart and indicate the need for additional experimentation.

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HLA types in South Africa

To the editor—Karen Birmingham's interesting article on the South African AIDS Initiative (*Nature Med.* **5**, 1220; 1999) states that "the predominant HLA types in South Africa are presently unknown." This ignores a succession of International Histocompatibility Workshops that have provided both HLA serological and molecular typing data for many sub-Saharan African populations.

Readers are referred to a recent article by Hammond and colleagues[1], which provides an extensive molecular HLA class I and II data on many South African ethnic groups.

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