PROPOSED CARDIOVASCULAR SCIENCES IRG
Summary of Web Comments and Letters

The Cardiovascular Sciences Study Section Boundaries Team met from October 31 - November 2, 2001 to draft the proposed guidelines made available for public comment on the Center for Scientific Review's (CSR) Web page. The guidelines were available for comment for a twelve-week period that ended in February 2002. The comments and letters received are summarized below:

COMMENTS ON OPTIONS FOR COMBINING STUDY SECTIONS

The commenters offered the following suggestions based upon the preamble to the Cardiovascular Sciences proposed guidelines. The CVS Study Section Boundaries Team discussed options should the review load for a proposed study section be too low to be viable. Two options were considered feasible: combining the integrative sciences of the proposed Clinical and Integrative Cardiovascular Sciences study section with the proposed Hypertension and Microcirculation study sections, leaving the Clinical Cardiovascular Science as a stand alone study section, or combining the proposed Vascular Cell and Molecular Biology study section with the proposed Hypertension and Microcirculation study section

- Of the options outlined, it would appear best to combine the Vascular Cell and Molecular Biology and Hypertension and Microcirculation study sections, as they appear most compatible.
- Vascular Cell and Molecular Biology will be very large. Adding Hypertension and Microcirculation to it would create an unwieldy group. The two do not fit together well and HM may go better with vascular development in terms of creating a good size.
- If a need exists to combine study sections, the stand alone clinical cardiovascular sciences study section option is best.
- A number of reviewers and applicants who submit proposals to the current Cardiovascular Clinical Research Study Section commented on what they perceive as the dissolution of the current Cardiovascular Clinical Research study section and replacing it with the proposed Clinical and Integrative Cardiovascular Sciences study section. There was general agreement amongst the researchers that their applications do not fair well when reviewed in the context of hypothesis-driven, basic research.
- CICS is the only proposed study section that would deal in any apparent way with integrative cardiovascular sciences, to include neural control of the CV system. This study section seems to be the only one in which basic and clinical studies will go "head-to-head" in competition for NIH support. One has to suspect that with the emphasis of CICS being clinical, that this unique situation will lead to a decline in an area of CV science.
- The potential unfairness of this approach was the specific focus of the Clinical Research Study Group's (CSRG) deliberations…CSRG's recommendations were strongly endorsed both by the Clinical Research Advisory Committee to the Director of NIH and by Congress as embodied in the Clinical Research Enhancement Act of 2000. The present configuration for review of clinical research applications, provides as more fair review for the reasons cited in the CSRG report.

- The UK has gone down the route of combining the review of clinical and basic research and it has decimated clinical research.
- Several comments were received in support of the creation of independent study sections for the study of animal models and integrative physiology.
- One group endorsed the descriptive statement for CICS, particularly those elements embodied in the first two sentences. Within the CVS IRG, CICS is unique among the other proposed study sections insofar as it is only one explicitly identifying integrative treatment of cardiovascular physiology as one of its primary charges.
- Paramount importance that there be at least one study section in the CVS IRG that is specifically charged with having substantial review expertise in integrative CV physiology at both the basic and clinical science levels.

STUDY SECTION SPECIFIC COMMENTS

Cardiovascular Differentiation and Development

Missing element within CDD, VCMB and CCHF – There needs to be acknowledgment of posttranscriptional regulation including mRNA stability, translational control, and post-translational modification including phosphorylation, lipid modification and ubiquitination. CDD only covers the topic in a developmental context, VCMB also focuses on transcription factors and promoter analysis and CCHF does not seem to address either of these regulatory mechanisms in the context of hypertrophy or failure.

Cardiac Contractility, Hypertrophy and Failure:

- Transplant-related proposals dealing with organ preservation, graft vasculopathy, and surgical techniques should be reviewed in IRG 21. Valvular heart disease as it relates to mechanisms of valve dysfunction and surgical interventions should also be in IRG 21. Surgery applications reviewed within the context of a non-surgical review body will not receive fair reviews. Non-surgeons lack both the surgical and technical expertise to properly critique surgery applications and would not be able to provide appropriate peer review.
- *Missing element within CDD, VCMB and CCHF* - The acknowledgment of posttranscriptional regulation including mRNA stability, translational control, and post-translational modification including phosphorylation, lipid modification and ubiquitination. CDD only covers the topic in a developmental context, VCMB also focuses on transcription factors and promoter analysis and CCHF does not seem to address either of these regulatory mechanisms in the context of hypertrophy or failure.

Electrical Signaling, Ion Transport and Arrythmias (ESITA) Study Section

- The statement, "Biophysical and other approaches to study the function of individual protein molecules," is very broad and some indication of the classes/types of individual protein molecules would be helpful. Also, it is questionable whether there are enough biophysical protein applications to allow them to be clustered in this IRG and still have a critical mass.
- Surgical interventions for the management of arrhythmias should be reviewed in IRG 21. Similarly, transplant-related arrhythmias should be kept together with transplant-related proposals in IRG 21. Surgery applications reviewed within the context of a non-surgical review body will not receive fair reviews. Non-surgeons lack both the surgical and technical expertise to properly critique surgery applications and would not be able to provide appropriate peer review.

Vascular Cell and Molecular Biology (VCMB) Study Section

- The need for a panel focused on Vascular Cell and Molecular Biology is increasing.
- VCMB does not offer much for vascular contractility and metabolism. The guidelines neglect the major function of differentiated smooth muscle, i.e. contractility. The later is also the end effector in many diseases such as hypertension. Metabolism, as it relates to cardiac ischemia and reperfusion injury, and the effects of hypoxia and oxygen-sensing mechanisms critical to pulmonary function were unmentioned.
- There is a critical shared interest with IRG 21 related to the areas of remodeling, angioplasty, restenosis, grafts, stents, etc., that was omitted in the guidelines. The vast majority of sciences related to the development of novel devices including artificial vascular grafts, stents, tissue engineered CV constructs, etc. falls outside the scope of CVS and lies more squarely with engineering which should be in IRG 21, while clinical evaluations of established devices would be in CVS.
- The study of the cellular and molecular basis of inflammation (innate immunity) is critical to our ability to enhance this process when we needed (e.g., an immunocompromised cancer or AIDS patient) and combat it with more effective and selective anti-inflammatory therapies. Leukocyte-endothelial cell interactions relevant to inflammation would appear to fit within the VCMB study section, but within the present description, would be insufficient for these types of applications.
- *Missing element within CDD, VCMB and CCHF* - The acknowledgment of posttranscriptional regulation including mRNA stability, translational control, and post-translational modification including phosphorylation, lipid modification and ubiquitination. CDD only covers the topic in a developmental context, VCMB also focuses on transcription factors and promoter analysis and CCHF does not seem to address either of these regulatory mechanisms in the context of hypertrophy or failure.

Myocardial Ischemia and Metabolism (MIM) Study Section

- There is no mention of blood-synthetic surface interactions or cardiopulmonary bypass within MIM, which is the only proposed study section that is remotely related to extracorporeal perfusion and blood non - endothelial cell surface interactions. Yet this area of inquiry offers prospects of long-term mechanical circulatory and respiratory assist devices, artificial internal organs capable of processing blood (e.g. artificial liver, kidney, lung, etc.) and prevention of thrombotic complications produced by any device placed within the blood stream.
- There is a great deal of overlap between this study section as it is currently defined, and ischemia/reperfusion studies in the context of cardiac surgery and cardiopulmonary bypass. The Boundaries Panel recognized this, but this aspect should be emphasized.
- Studies relating to myocardial metabolism as it relates to organ preservation in transplantation or cardiac surgery should be reviewed by IRG 21. Surgery applications reviewed within the context of a non-surgical review body will not receive fair reviews. Non-surgeons lack both the surgical and technical expertise to properly critique surgery applications and would not be able to provide appropriate peer review.

Hypertension and Microcirculation (HM) Study Section

Structural changes in the vascular system are an important aspect of hypertension (e.g. increased peripheral resistance and microvascular rarefaction). It is suggested that "structural adaptation and remodeling of the vascular system" should be included in the list of specific areas covered by the HM Study Section. The nearest alternative is in the CDD study section, but the structural adaptation occurring in hypertension is not adequately described.

Arteriosclerosis and Inflammation of the Cardiovascular System (AICS) Study Section

- The AI descriptions related to sepsis appear to claim all of it. The guidelines need to be specific about endovascular infections and their consequences on the heart independent of the surgical aspects. It is critical to recognize that sepsis and endotoxemia are systemic in nature affecting all organ systems and no single organ in isolation.
- Proposals that focus on sepsis endotoxic shock and septic shock should not be assigned to CVS. Such systemic inflammation is confined to neither the heart nor the vasculature, but affects all tissues. It involves multiple organ systems and interactions. In contrast, cardiogenic shock (a disease process that reflects pump failure), and inflammatory processes that are limited to the vasculature (e.g., atherosclerosis and the vasculitides) are highly appropriate for review within CVS.
- The current SAT study section should remain intact and review transplant immunology-related applications that deal with vascular/cardiovascular issues.
- Cardiopulmonary bypass results in severe inflammatory response which modulates the effects of ischemia/reperfusion and activation of the clotting cascade in surgical patients. Proposals that aim to understand these complex interactions are best reviewed by the individuals familiar with the effects of bypass and who understand the relevant issues. These types of proposals are best reviewed in the surgery IRG where reviewers are familiar with this type of inflammatory process.
- Applications involving sepsis, endotoxic/septic shock and cardiac transplant immunology should not be reviewed in the Atherosclerosis and Inflammation Study Section, and belong in the Surgical Sciences study sections. Thus, placing these applications within the AICS study section ignores the systemic impact of the event.
- There are specific areas currently covered within the AI study section that are more appropriate for VCMB: Signaling in the vascular wall; cell signaling influencing the vessel wall; nuclear hormone receptors; Peroxisome Proliferator Activated Receptor (PPAR) and Liver X Receptor(LXR); and sterol and fatty acid ligands.

Clinical and Integrative Cardiovascular Sciences (CICS) Study Section

- The statement that “Human studies ranging from exercise and neural control to clinical studies of mechanisms and consequences of disease”, should be amended to include animal models.
- The statement that “Both acute responses and training adaptations are included” should clarify that this includes both normal and cardiovascular disease states.
- Revise, “Human and animal models investigating the influence of acute and chronic exercise on cardiac and vascular, heart muscle, neural, humoral, and regional circulation may be included” to read, “Human and animal models investigating the influence of acute and chronic exercise on cardiac and vascular smooth muscle, neural and humoral systems involved in cardiovascular regulation, vascular endothelial function, specific regional circulations, and gene expression in cardiovascular system may be included.”
- MIMS (and ESTA) do not specifically address the effects of exercise stress on model systems of interest. Add, “In addition, studies of the adaptive responsiveness cardiac mechanical, contractile, and metabolic function to acute and chronic exercise in both human and animal models should be reviewed in CICS" to the shared interest statement.
- Neither CCHF nor VCMB specifically address the effects of exercise stress on the stated issues of interest. Add, “Calcium regulation and signaling. Applications addressing the effects of acute and chronic exercise on endothelial and cardiac and vascular smooth

muscle calcium regulation and receptor-mediated effects restricted to cell growth signaling, contractility, apoptosis, and remodeling are appropriate for review by CICS."