# *apsf* Anesthesia Patient Safety Foundation

**Meeting Report**
**Anesthesia, Surgery, and Long-Term Outcomes**
**September 21-22, 2004**
**David M. Gaba, M.D., Conference Principal Investigator**

Anesthesiologists have long been pioneers in seeking ways to improve the safety of patients. Indeed, the mission statement of the Anesthesia Patient Safety Foundation (APSF) is "… to ensure that no patient shall be harmed by anesthesia." To-date, most of our efforts have been on reducing the likelihood of adverse events in the immediate perioperative period. Many of these events can be traced to errors of individuals, teams, or the system of care. Over the last few years several threads of information have been coalescing that suggest there is another sort of patient safety issue, by which patients may suffer from the effects of anesthesia and of surgery. This has to do with adverse outcomes occurring remote from the perioperative period (which typically stretches no further than 30 days from the procedure), and which are not directly tied to a specific complication of the surgery. Generically these might be referred to as "long-term outcomes" of anesthesia and surgery.

The APSF has started to take an active interest in this topic. In two recent issues of the APSF Newsletter (Fall 2003 and Spring 2004) a number of these issues were discussed in overview, along with the hypothesis that the underlying biological mechanism to explain the occurrence of such long-term outcomes might have to do with inflammatory processes triggered in the perioperative period. As detailed in those Newsletter articles there are a variety of reasons to think that mortality, and presumably morbidity, can be affected by perioperative events, and that inflammation could be a key element in such occurrences.

Because the threads were disparate, from different medical domains, and still uncertain, the APSF decided to convene an experts' workshop to discuss these issues. I was selected as the principal investigator for the workshop because I am an experienced researcher, a patient safety expert, and the secretary of the Foundation. Yet, I do not conduct research in this area, nor have I had any specific interest in this topic until it came to the attention of the APSF.

Thirty experts attended the conference in Boston, MA, September 21-22, 2004. The names of attendees and their biographies are available on the APSF Website. The program was divided into four sessions. I) Epidemiology of long-term outcomes following anesthesia and surgery; ii) two sessions on inflammatory processes and other underlying biological mechanisms; and iii) a final session reviewing the issues discussed, the pitfalls of conducting outcomes research, and debating the best course of action for future research. The full program for the workshop is also available on the APSF Website.

After a welcome by Robert K. Stoelting, M.D., President of the APSF, I presented the goals for the conference:

* Define the problem(s) of long-term outcomes after anesthesia & surgery
* Estimate the scope and nature of the problem(s)
* Assess the state of play of the science of the putative inflammatory mechanisms
* Identify the most important research questions, and the key gaps between what is being studied and what needs to be studied
* Develop an agenda for possible research
* Determine if existing interventions require greater attention for evidence-based guidelines/practice parameters
* Identify new interventions in need of study
* Develop a plan for dissemination and follow-up

**Session 1: Epidemiology of and Risk Factors for Long-term Outcomes**

Robert Lagasse, M.D. began by reviewing some of the history of research on short term adverse outcomes in anesthesiology, to illuminate issues in studying long-term outcomes. Of note, even seemingly obvious short-term outcomes have been difficult to define precisely, leading to inconsistencies between different studies. Dr. Lagasse suggested that the advent of Anesthesia Information Management Systems (AIMS) could make it easier to link intraoperative events to both short-term and long-term outcomes. One particular pitfall is the relative lack of sound risk-adjustment models to assess outcomes independent of the many underlying variables that can affect them.

Next, Shukri Khuri, M.D. described the Veterans Health Administration's National Surgical Quality Improvement Program (NSQIP). Dr. Khuri is a cardiac surgeon who has led the NSQIP project for many years. NSQIP tracks surgical outcomes (typically out to 30 days post-op) for a number of major surgical procedures in a variety of surgical specialties, across all VA facilities that perform them. The NSQIP database depends on data entered by a specially trained nurse at each site, who is able to leverage the VA's electronic medical record system. Data are collected on a large number of pre-operative variables, on a few intraoperative variables (e.g. duration of surgery, surgical procedure), and then on a suite of post-operative outcome variables. Over the years the NSQIP project has produced a highly sophisticated risk-adjustment model that has also been validated for patients in the private sector. Based on this model the NSQIP program computes "observed to expected ratios" for the different adverse outcomes for each VA facility. This allows identification of both good outcome outliers as well as negative outcome outliers. The former can be studied for lessons learned, while the latter receive focused attention on issues they can improve. In addition, the Department of Veterans Affairs provides death benefits for all veterans, and thus keeps records of patient deaths that can be linked to the NSQIP records, allowing tracking of long-term outcomes. The NSQIP database now has more than 1.2 million records and for selected patient groups has assessed mortality out to 10 years. The NSQIP program has been expanded to the private sector, first in a set of studies and now in a joint program with the American College of Surgeons – ACS-NSQIP.

Finally in this session, Terri Monk, M.D. discussed the history of studies of long-term mortality following anesthesia and surgery in different patient populations. She provided an overview of

intervention studies such as those using beta-blockade in the perioperative period. She also presented provocative but very preliminary data from her own studies (Weldon & Monk, et al.) of perioperative cognitive dysfunction in patients having general anesthesia. Data on intraoperative vital signs (including heart rate, blood pressure, and BIS value among others – although the BIS value was only recorded and was not seen by the anesthesiologist) were recorded for these patients as were various post-operative outcomes, including mortality at one year. The data on mortality were then subjected to Cox hazard multiple regression modeling to determine which underlying pre-operative and intra-operative factors correlated with death at one year. Not surprisingly, underlying medical problems (Charleson co-mordity score of $\geq 3$ vs. $<3$ was by far the major risk factor (Odds ratio 16.1), as was time spent with a systolic blood pressure less than 80 mm Hg (Odds ratio 1.04 per minute < 80). Also a significant risk factor falling out of the multiple regression was time spent with a BIS value < 40 (Odds ratio 1.24 per hour with BIS<40). At the time of the Workshop a paper describing this study was in-press in Anesthesia & Analgesia; in January, 2005 it was published (along with an editorial): Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100: 4-10; Cohen NH: Anesthetic depth is not (yet) a predictor of mortality! Anesth Analg 2005 100: 1-3.

Dr. Monk described results of a similar study performed on a larger number of patients in Sweden that also showed that BIS < 45 (the chosen threshold in this study was 45 rather than 40) fell out of the regression as a statistically significant risk factor (Odds ratio 1.20). Unfortunately the authors of this study (Drs. Lennmarken and Sandin) were not able to attend the conference. A follow-up of the Swedish data with mortality to 2 years still showing a statistically significant effect of time with BIS<45 will be reported at the 2004 ASA scientific session, as will a case-control analysis of the data. Dr. Monk described all of these results as surprising, since there was no obvious mechanism to account for these findings. In addition, approximately one half of the deaths in her study were due to cancer, and the correlation of time with hypotension or with BIS < 40 to death due to cancer was even harder to explain.

***Discussion of session 1.***

Robert Stoelting, MD chaired the discussion of session 1, at which the panel reviewed the epidemiology extensively. There was particular focus on the data from Weldon and Monk's study and from Lennmarken et al, because these results were unexpected. It was acknowledged that these data are preliminary and are strictly observational, and the full descriptions of both studies have not yet been published in peer-reviewed journals. Nonetheless, they are provocative data, as they suggest that some factor occurring during the brief period of the anesthetic is linked to mortality remote from the peri-operative time frame.

There was spirited debate about these data and what they could mean if they are confirmed with further studies. One suggestion was that the occurrence of BIS<45 represents merely a marker for patients who are particularly vulnerable for some reason. One possibility advanced was that they have a higher adrenergic state and are treated with higher levels of hypnotics or volatile anesthetics. It was also suggested that, given the other threads (see sessions 2 & 3 below) concerning inflammation, the patients with the low BIS values might have a greater or more extended inflammatory response to anesthesia and surgery, although there are no studies yet that have investigated such a putative mechanism.

It was widely agreed that even when the two studies that concern BIS values are published in full, such surprising findings would probably need to be confirmed in larger studies that specifically investigate this issue. Such studies would need to measure and control for many other factors in anesthesia management, such as intra-operative medications (including the changing levels of volatile anesthesia). Some suggested that previous or future studies of outcome for patients having general anesthesia versus regional anesthesia would be important benchmarks relative to the surprising findings concerning the BIS value.

There was additional discussion of other perioperative factors and treatments that have an impact on long-term outcomes. In particular, the data on perioperative beta-blockers is complex. While there have been multiple randomized trials, and there is a consensus for beta-blockade for patients with known cardiac disease having vascular surgery, whether this is beneficial for broader use is still open to considerable debate. The recently published study of beneficial outcome effects of perioperative clonidine in high-risk patients is interesting because it involved only 4 days of treatment, but the study was small and cannot be considered definitive. Nonetheless, a number of these studies suggest that treatments only in the perioperative period (a few days to weeks) can have long-lasting effects.

**Sessions 2 and 3 – Inflammation**

Potential biological mechanisms for such occurrences were the topics of sessions 2 and 3. At the beginning of session 2, Dr. Steffen Meiler proposed a set of hypotheses concerning the perioperative inflammatory/immune response as a potential biological link to long-term outcomes after anesthesia and surgery. Dr. Meiler proposed a "two hit" model which states that the inflammatory response to surgery may amplify pro-inflammatory cell mechanisms of certain disease states, such as coronary artery disease and hence contribute to disease acceleration and adverse postoperative events. The evidence that inflammatory processes are critical for the progression of atherosclerosis is undeniable. Similarly, inflammatory processes and infections are known to play a key role in cancer biology (e.g. hepatitis leading to hepatocellular carcinoma). The role of inflammation with the degenerative central nervous system diseases, such as Alzheimers, is more tentative, but a growing body of evidence definitely points in this direction.

Furthermore, Dr. Meiler proposed that certain patients or patient populations may exhibit an exaggerated inflammatory response to surgery and/or delayed resolution to the preoperative immune status. Limited human data are in support of this notion. If true, these patients may be at even greater risk to experience postoperative complications. What would cause an abnormal inflammatory response to surgery is not known, nor are all the factors that might be triggers beyond the surgical procedure itself. Whether anesthetic drugs, other aspects of anesthetic technique, or physiologic occurrences during surgery could be potent triggers for abnormal inflammation is not well established. There are threads of evidence that anxiety, fear, and pain can trigger inflammation.

This led Dr. Meiler to propose that perioperative care is a key nexus for affecting both short-term and long-term outcomes. A commonality between anesthesiologists, surgeons, internists, and

others will be to identify which patients are at risk, to define adjuvant treatments and modified patient care processes to prevent the negative outcomes, and to apply them throughout the continuum of the perioperative period. According to these models, taking an inflammation/immune-based approach to dissecting the biological interactions between anesthesia, surgery, and postoperative complications therefore promises to yield important insights.

Clinton Webb, PhD, a physiologist presented on the role of inflammation in atherosclerosis in animal models. He noted that inflammatory markers interleukin-6 and CRP are associated with hypertension. Norepinephrine triggers production of IL-6 mRNA in a dose dependent fashion in cell cultures of rat fibroblasts. IL-6 potentiates the response to other vasoconstrictors as well. It potentiates the effects of angiotensin II in wild-type mice. Dr. Webb described experiments with cage stress, a standard test in mice – when put in a cage that had been occupied by another mouse they explore more to find the source of smell. With cage stress the IL6 knockout mice have a greater temperature response than do wild type; their heart rate is no different, but they have a markedly decreased blood pressure response to the wild types. Dr. Webb speculated that aspirin might be usable as an antihypertensive if it reduced the release of IL6 or other cytokines. The overall implications of this research is that changes induced in the inflammatory state could have major effects on the cardiovascular system when such changes are not resolved within a short amount of time. Potentially, a prolonged inflammatory state could induce hypertension and arteriosclerosis.

Last in the session, Rod Eckenhoff, M.D. discussed the effects of volatile anesthetics on the oligomerization of brain proteins. This line of research was triggered by the speculation that many neurodegenerative diseases may be caused by the aggregation of normal and abnormal proteins (similar to what occurs in Mad Cow Disease). Halothane and other volatile anesthetics do cause oligomer formation in amyloid precursor protein at clinically relevant levels, and this process lasts a long time. A single exposure of desflurane caused 3 days of differences in protein expression. Other proteins could be affected similarly. One example cited is ferritin, which binds volatile anesthetics at low concentrations. New animal models are being established in rats, which are thought to be a better model system. Finally, although these mechanisms suggest that exposure to volatile anesthetics might be linked to the occurrence of dementia, this conclusion at this point is very speculative, Dr. Eckenhoff indicated his collaboration with the outcomes researchers in his institution to conduct a study of the Medicare database attempting to correlate the occurrence of dementia and prior anesthetics.

***Discussion of Session 2:***

The discussion was led by Dr. Carl Rosow. There was extensive discussion about what is meant by "stress," and whether "anxiety," "stress," or other terms really describe the same state. There was further discussion of the diverse responses and time-frames of inflammatory responses that were being discussed. Some inflammatory response is critical for wound healing and warding off surgical infection, yet too much, or too prolonged a response might be deleterious.

The Panel tried to determine whether any existing studies show a definitive link between the kinds of inflammatory mechanisms suggested and post-operative complications. Some threads

were drawn from studies of patients having cardiac surgery and cardiopulmonary bypass, but it was acknowledged that no studies to-date demonstrate this putative linkage specifically. There was discussion of whether one could study the long-term outcome of animals (rodents in particular) that had undergone anesthesia and surgery, while studying their inflammatory responses. It was suggested that the kinds of genetic variants being made in the laboratory (e.g. "knockout" mice) would allow various pathways to be studied. Other panelists cautioned that the experience with animal models in sepsis and other conditions in critical care suggested a limited ability to extrapolate to humans, although the animal studies could be important in assessing potential avenues of intervention. There was wide agreement that understanding the subtle issues of long-term outcomes would require both animal studies and human studies.

Building on this, there was extensive discussion of how to develop control groups for studies of long-term outcomes and of perioperative interventions. Under what circumstances is it realistic to expect a control group of matched patients who do not undergo anesthesia and surgery? Some such studies have been done in the past, but it is difficult to determine the selection bias imposed by comparing patients having surgery vs. those who are not. It was pointed out for example that some drugs do not have parenteral formulations, thus excluding patients who cannot take drugs orally (a common occurrence in the perioperative period).

The Panel's attention returned to the studies from Monk et al, and Lennmarken et al discussed in the previous session (concerning outcomes related to time with BIS<45 for example). There was extensive discussion of how one would best design studies to investigate more fully and possibly confirm these preliminary findings. The issues revolved around whether it would be necessary or possible to control the type and amount of different drugs used, or to have different modes of anesthesia utilized (e.g. volatile anesthesia versus total intravenous anesthesia). In addition, Dr. Rosow suggested that beneficial or deleterious effects of pharmacologic interventions should bear some relationship to dose, yet surprisingly little dose-response information is available. Perhaps BIS<45 is an indirect measure of anesthetic dose. It was pointed out that one step forward from the existing preliminary data would be observational studies of how anesthesiologists actually conduct their anesthetics, measuring the drugs actually administered vs. the hemodynamic responses as well as EEG measures (either hidden or not). Such observational studies could be linked to long-term outcome measures (such as mortality) and at the same time to tracking biomarkers of inflammatory response.

**Session 3: Inflammatory Mechanisms Redux**

Session three continued the theme of looking at basic biological aspects of inflammatory mechanisms. First, Charles Serhan, M.D. presented a fascinating description of the active processes that resolve inflammation after it has been triggered. This resolution is not just a "burnout" of the pro-inflammatory functions, but rather has a set of resolution functions that involve resolving mediators. Resolution is thus different than merely "anti-inflammation" and the resolution processes offer another potential target for therapeutic manipulation. Furthermore, anti-inflammatory therapies may sometimes also inhibit the natural pro-resolution pathways, thus delaying or blunting their beneficial effects.

Dr. Serhan first reviewed the standard picture of the acute inflammatory process. Initial infiltration with neutrophils is followed by infiltration with non-pro-inflammatory monocytes. He then described the mechanisms for inflammatory resolution. Many of the mediators of the resolution phase are lipid mediators, among which are lipoxins, resolvins, neuroprotectins,. Some of these can be generated preferentially in the presence of aspirin. This research has involved many methods, including periodontal models of inflammation, and the "mouse pouch" model. The resolving molecules are very potent inhibitors of "inflammation" through their promotion and speed-up of the resolution processes. Resolvins may be the active ingredients of the beneficial effects of Omega3 fish oil and other dietary elements. Similar molecules in the nervous system are called neuroprotectins. In some animal models, such as rodent peritonitis, long acting mimetics of resolvins and related molecules can reduce the maximum inflammatory spike, and markedly reduce the elapsed time to achieve a 50% drop in the number of polymorphonucleocytes in the peritoneal fluid.

Dr. Serhan summarized the potential promise of this line of investigation as offering ways to mitigate the negative effects of inflammation by turning on resolution rather than by attempting to inhibit the pro-inflammatory phase itself. However, turning this basic science into therapies ready for clinical trials will take some time.

Next, Andrew Lichthman, MD, PhD discussed adaptive immunity, chronic inflammation, and chronic disease. Wherease Dr. Serhan's investigations have focused on modulating acute inflammatory reactions, Dr. Lichtman has been studying more chronic processes that tend to involve lymphocytes rather than PMNs. In fact, he noted that such chronic inflammation can occur without there ever have been a precursor of clear-cut acute inflammation.

He noted that it is widely accepted that atherosclerosis is clearly an inflammatory disease, and not just a "lipid-storage disease." He reviewed some of the evidence in animals and humans linking elevations of inflammatory markers – in particular C Reactive Protein – with the occurrence of atherosclerotic disease.

He then reviewed a large set of studies concerning the various mediators of atherosclerosis in mouse models which are made hypercholesterolemic by combination of genetic manipulation and special diets.

***Discussion of Session 3:***

Don Stanski, M.D. chaired the discussion of Session 3. There was extensive discussion of how to find the middle ground between the elegant basic science work and the interface to the clinical issues of long-term post-surgical outcomes. One thread discussed was to find the best markers – perhaps novel ones rather than those such as CRP that had previously been used – to be monitored throughout the pre-, intra-, and post-op phases, against which to correlate with short and long-term outcomes. In this regard, there is some work going on to develop more easily run assays for some of the resolution molecules.

Another thread was trying to better link up the seemingly beneficial effects of drugs like beta-blockers, clonidine, statins and the underlying bioactive mediators.

An interesting question was raised as to the effects of discontinuing patients' aspirin or non-steroidal anti-inflammatory therapies prior to surgery so as to minimize their effects on platelet aggregation, and thus on perioperative blood loss. A side effect of stopping these drugs could be to promote or unmask a more extreme inflammatory response.

There was speculation that some studies of the effects of anesthetics, of surgery, and of the combination of the two could be studied in the same rodent models for which the immunology can be studied in detail. However, in many of the existing immunology studies it is necessary to anesthetize the rodents for certain procedures, and these anesthetics might be introducing confounding variables into those studies. A number of panelists questioned whether studies of anesthesia and surgery in rodents would have much value in extrapolation to humans.

It was pointed out that there are a number of interventions that have been studied in the perioperative period that have effects beyond those typically investigated. Although a recent meta-analysis showed no effect of pre- vs. post-procedure administration of analgesics, the continuous prevention of inflammatory responses during the perioperative period through analgesia ( perhaps termed "preventive analgesia" rather than "preemptive analgesia") may well prove beneficial. Outcome benefits have also been shown with short-term intra- and post-operative lidocaine infusions. The latter has been shown to speed the return of bowel function and shorten hospital stay in patients having radical retro-pubic prostatectomy. A generic follow-up to these kinds of findings is the notion that some drug treatments seem to have effects – perhaps through immune modulation – that last much longer than the drug's therapeutic levels in the body. Whether such therapies would also alter long-term outcomes such as mortality has not been studied. A general thread of the discussion was whether it would be worthwhile to develop robust methods to acquire long-term mortality data from patients who participate in trials of short-term interventions for short-term benefits.

While some advocated using wound infection as a surrogate marker for an indirect outcome (as distinct say from cardiovascular events) others felt that this was confounded by direct surgical factors, and also that in the NSQIP data, wound infection was not a major predictor of longer term mortality. The most significant short-term complication in terms of predicting a long mortality was a respiratory complication within 30 days of surgery. It was noted that even minor wound infection was easier to diagnose than was a minor respiratory complication, and thus those having a respiratory "complication" were in fact having a very significant event almost by definition. Nonetheless, in terms of searching for complications to address that have the greatest impact on long-term outcomes, any means to reduce the respiratory complications offer the most potential long-term benefit.

Additionally, there was considerable discussion about whether it is beginning to be possible to tease out which patients are most susceptible to short and long-term negative outcomes on the basis of their genotype, or biochemical markers, in addition to the traditional risk factor analysis.

**Session 4: Wrap Up**

Jeffrey Cooper, Ph.D. chaired Session 4. He started by reviewing the interest of the Anesthesia Patient Safety Foundation in the topic of long-term outcomes. He again reminded the audience that the mission statement of the Foundation does not limit itself to the immediate perioperative period. He posed several questions for the group to resolve:

- What, if anything, can the panel agree on?
- Do we have a definition of a long-term outcome?
- Are there effects of anesthesia and surgery on long-term outcomes?
- What hypotheses need to be tested?
- Should APSF as an organization continue to pursue this area as an ongoing initiative, or should we let other organizations and mechanisms take this on without the Foundation's involvement?
- Should this conference be a "one-time" event, or should APSF consider a follow-up meeting in one or two years?
- What "publications" or other dissemination vehicles should come from this meeting and by what process should they be vetted by the participants?

Dan Sessler, MD, and Lee Fleisher, MD then each provided some advice on the opportunities and pitfalls concerning outcomes research. Dr. Sessler discussed in particular the complex infrastructure needed to conduct outcomes research, and especially concerning long-duration studies of long-term effects. He noted that if such trials are attempted without the right infrastructure in place they can collapse and waste the resources invested. The infrastructure includes expertise and experience in working together in areas such as: finance, regulatory issues, statistics, databases. He suggested that many investigators and institutions do not have well-functioning trials' teams in place to provide this support.

Dr. Fleisher noted that in cardiology, many of the key trials involve 20,000 to 30,000 patients, whereas even the largest randomized trials discussed at this workshop involved far fewer patients. As such, the excess mortality of one group versus another many only be a few patients. He also suggested that while the analysis of administrative databases can be useful for some purposes, it may be difficult or impossible to use to answer many of the questions that have been raised at this conference.

He then suggested a model that might drive our thinking about what we know and what needs to be done. We know that there are patients at risk. They are exposed to stressors of surgery and anesthesia that may "do something" (what exactly we do not yet know) that causes in some of these patients adverse occurrences post-operatively at various different time points (e.g. 1 day, 30 days, a few months, 1 year, 2 years, etc.). It is hard to tease out from this sequence what is the contribution to the "etiology" of the risk factors, the stressors, the mechanism of what happens, and the factors that affect who then goes on to actually develop a palpable negative outcome. He suggested that different mechanisms might be at play for different outcomes at different time points.

He noted that he and others had attempted to generate interest for various sorts of randomized trials of technology or interventions. For example, his exploration of a trial of high levels of

anesthetic depth vs. light level of anesthesia on various outcomes was of no interest to NIH, and a proposed trial of statin therapy on long-term outcomes was of no interest to the manufacturers of those drugs. He also suggested that if intervention studies are done, consideration should be given to assess dose-response rather than to just evaluate treatment vs. no-treatment.

There was then discussion of how the NSQIP work could be expanded to help acquire more observational data. NSQIP could be linked to intraoperative physiologic and pharmacologic data via AIMS systems where they are in place. It can be linked to pre and post-operative medications through the pharmacy database. Finally, it was suggested that, if appropriate biomarkers (e.g. IL-6, CRP, etc.) levels could be measured in the perioperative period, those data should be added to other data now being entered in the NSQIP database.

Karl Hammermeister proposed a "straw man" sequence of investigations to be considered by the panel. This sequence is:

- Confirm excess late adverse outcomes (e.g. mortality)
- Identify predictors of late adverse outcomes
- Evaluate mechanisms of excess late adverse outcomes
- Conduct small-scale trials of interventions for excess late adverse outcomes
- Conduct large-scale comparative randomized clinical trials of interventions

He then provided some more detail for each of these steps:

**Confirming existence of excess late adverse outcomes**

This would require one or more large-scale observational studies. He suggested trying to compare the outcomes for routine and expectedly "curative" surgery (e.g. something like cholecystectomy) with a control group of non-operated patients with similar co-morbidities. It was pointed out that for many disease processes the differences between those who choose surgery vs. others may be significant confounders, but it is possible that comparative populations do exist for some procedures. Others suggested that a non-operated control group might not be necessary, in that it might only be necessary to show in larger populations that certain perioperative factors or occurrences were associated more frequently with late adverse outcomes.

While a complete analysis of what characteristics one or more studies would need to confirm the general phenomenon, or to confirm the surprising findings of Weldon, Monk, et al., or of Lennmarken, Sandin, et al., a number of suggestions were made about ways that future studies might be improved.

- First, studies with more than a few thousand patients might be necessary.
- Second, the list of perioperative factors that would need to be recorded should include (but not be limited to) a number of items that were not apparently included in the existing studies, e.g.:
  - Anesthetic depth
  - Type of anesthesia
  - Perioperative medications
  - Intraoperative physiological data
  - Data on glucose and glucose control

Occurrence of other interceding complications
The level of inflammatory markers at different perioperative time points (see next section)

- Third, the factors such as blood pressure and BIS that were assessed in terms of duration below a threshold value might be assessed also in other ways that use different thresholds or use non-threshold variables (e.g. time-weighted average) to determine whether these factors are robust to small perturbations in the definition of the variables or thresholds, and not due to any artifacts caused by the definition.

Fourth, factors related to EEG variables might be assessed more generically by recording raw EEG and then applying different published or proprietary algorithms to derive several EEG-based variables. If the correlations with long-term outcomes is robust, one should see an it with more than one type of EEG analysis algorithm.

Fifth, more sophisticated statistical modeling techniques might be needed to look at the larger set of complex variables that would be included in the analysis.

**Observational Studies of the Time Course of Putative Mechanisms**

A step that might be conducted in parallel would be a large observational study of the time course and risk factors for the rise and fall of inflammation as triggered by different combinations of anesthesia and surgery. This would presumably involve measuring inflammatory markers prospectively beginning in the preoperative period and extending long into the post-operative period. These data could then be correlated with the adverse outcomes, and also backwards to see which patient risk factors best predicted the change in inflammatory markers.

**Comparative randomize clinical trials of interventions, using all cause mortality as endpoint**

**Possible candidates for such studies might be:**

- Beta blockade and statins. He suggested a two-by-two matrix study of both therapies in concert. Having four arms of the study would require a large patient population.
- Type and depth of anesthesia – groups might involve general anesthesia vs. regional; general anesthesia with volatile anesthetics vs. no volatile anesthetics; and use of EEG monitoring to maintain hypnotic levels neither excessively deep nor light. Again, with so many treatment options, one would need either very large trials with multiple arms, or multiple trials..
- Alpha2 agonists such as clonidine and dexmedetomidine could be added to these trials, or involved in larger separate trials.
- Other interventions for study for long-term outcomes would be maintenance of normothermia, and tight glucose control.
- Evolving immunology data might suggest other novel modifiers for trials.

At this point, Dr. Cooper called for three "mini-votes" of the participants:

• ***Do you believe that there IS some relationship between inflammatory processes in the perioperative period and long-term survival?*** A majority of participants voted yes.

• ***Should an appropriate study be done to measure "excess" mortality resulting from identifiable factors of anesthesia and surgery?*** Again, a majority of participants voted yes.

• ***Should such a study demonstrating "excess mortality" be completed before any other studies – such as those suggested in the "straw man" – are begun?*** Only a few participants voted yes.

Marcel Durieux, MD, PhD expanded on Dr. Hammermeister's straw man. He advocated conducting campaigns of basic research and clinical research in parallel, since useful clinical investigations can be done even before the underlying mechanisms are fully defined in the laboratory.

Among the basic research questions and arenas to be addressed would be the following:

Is there persistence of inflammatory or other physiologic "memory" after surgery? That is, do any effects persist over a long time, well after any anesthetic drugs or surgical trauma are have resolved? As likely as this hypothesis seems, it has not been demonstrated to occur.

Develop animal models for studying long-term outcomes

Determine the optimal "inflammatory profile" that creates the proper balance between pro-inflammatory and anti-inflammatory factors. He noted that inflammation is a crucial element of wound healing. Hence, inflammatory suppression cannot be the goal, rather, some more subtle type of modulation will probably be necessary.

Studying the **interactions** of various perioperative interventions

Among the clinical questions that currently seem to ready for investigation, he listed:

*Relationship of EEG measures intraoperatively to long-term mortality.* The panel largely agreed that the data discussed so far are intriguing but very preliminary. Dr. Durieux re-iterated the need to see the data when they are published in full, and then to determine if further observational studies are necessary (perhaps with improvements as suggested by some panelists and summarized above). He emphasized that the issue is not necessarily "deep anesthesia" but that this might be a marker for patients who have different underlying physiology. In essence, what the preliminary data show is that some patients, who have an increased clinical requirement for anesthesia or an exaggerated EEG response to the anesthetic drugs they received, show increased long-term mortality. What we need to find out is what causes this increased requirement or exaggerated response.

*The development of chronic pain after surgery, and use of "preventive analgesia"to prevent this*

*Perioperative transfusion* and its effect on long-term outcome

*The development of a perioperative hypercoagulable state, which may result in Thromboembolism and/or myocardial ischemia.*

Dr. Durieux also noted that a major issue will be to develop implementation mechanisms for those practices that are demonstrated to be of value. The use of beta-blockade is still not uniform, even for patients with known cardiac disease and having vascular surgery for whom the therapy has been definitively recommended by consensus panels. There was extensive discussion of how the health care system might need to change to create optimal post-surgical outcomes. When does the "episode" of "surgical care" begin and end? Perhaps the "disease management" model is appropriate, such that a single disease manager would coordinate care across a long continuum from before surgery and last well after it was completed.

Some suggested that it would be best to do very focused studies on high-risk patients. For example, one could study whether beta-blockade affects 1-2 year mortality in a cohort of high-risk patients having non-vascular surgery, and in whom one measured a variety of inflammatory markers. This would allow, within a few years, to determine whether the hypothesis linking inflammation to negative outcomes was true.

Some comments were made about possible follow-up activities stemming from this conference. Dr. Khuri indicated that NSQIP is very interested about incorporating AIMS data in NSQIP. Dr. Hunt from CMS indicated that CMS might well be interested in adding additional variables to the database analysis projects that are currently in design.

The panel discussed the mechanisms and vehicles for disseminating its deliberations. There will be reports of the meetings occurrence and discussions prepared for the APSF Web Site, the APSF Newsletter, and for submission to several medical journals. These reports will be circulated to panelists for review and input prior to publication or dissemination, first in small groups, and ultimately to the entire group.

The possibility of an edited monograph of contributions from different authors was discussed. Dr. Fleisher suggested that the Anesthesia Clinics of North America, of which he is the editor, might be a venue for such a monograph. Contributions to such a volume would reflect the views of their individual authors, rather than of the panel as a whole.

Topics discussed might similarly be appropriate for large review articles for publication in scientific journals. This would be up to individual authors to decide.

Dr. Russell, the Executive Director of the American College of Surgeons, said that it was very clear that the entire team caring for a surgical patient – surgeon, anesthesiologist, primary care physician, cardiologists, oncologists, and many others – needed to engage in serious new efforts to share and coordinate their knowledge, perspectives, and clinical efforts in order to optimize outcomes for the patients. Never again could they satisfy themselves to work solely within their own silos, no matter how expertly.

*In summary, the group arrived at a number of threads of agreement and observation, which will now serve as the basis for future analysis and action. These include:*

1. *Historically, surgeons and anesthesiologists have largely felt their actions only have immediate or near-term consequences. Things not directly related to the surgical procedure that occurred "way down the line" (the "long term outcomes") had to do with the patient's underlying medical conditions and were just bad luck. But the group thought it was distinctly possible that there are things that happen during surgery that have lasting effects and may have a long-term impact on how long you live.*
2. *The group acknowledged that there may in fact be excess mortality over the long-term linked to the process of anesthesia and surgery. But the data are extremely sparse, complicated and have many limitations and pitfalls. The question should be pursued further to find a more solid answer.*
3. *There should be more studies of large numbers of patients to better identify risk factors for the occurrence of adverse long-term outcomes as well as for short-term complications.*
4. *Inflammation has been implicated in many disease processes and it is definitely possible that there exists a relationship between inflammation and the long-term outcomes associated with surgery and anesthesia. But much remains to be determined to see if this linkage is present, and if so its strength and what can be done about it. Studies are needed both on the basic biology of inflammation, and on the specifics of this biology in the setting of anesthesia and surgery.*
5. *As better data come in about the nature of outcomes after anesthesia and surgery, studies are needed to evaluate the mechanisms, and define possible interventions. This may happen first in small-scale trials, but ultimately large-scale studies with thousands of patients will be needed. Even for treatments that have already been looked at to minimize cardiovascular complications after surgery for high-risk patients with known heart disease, for example , beta blockade, we had a spirited debate about whether the studies done to date are just too small to be sure whether treating large numbers of patients is justified*