2018 PRESIDENT'S SUMMATION

I recently heard that the human brain borders genius up to the age of 4 years, which incidentally coincides with the time when children are placed in classrooms where they may not be encouraged to think freely and to question conventional wisdom. In fact, some estimations suggest that as academic knowledge increases over time, creativity takes a hit. In times when disagreements often lead to resentment instead of a healthy debate, it was refreshing to spend a weekend listening to presentations that were provocative enough to challenge dogmas in order to free our minds for creative thinking.

Dr. Alan Dove walked us through 75 years of history to remind the seminarians of the initial steps that were taken to unravel the mysteries of the genetic code that paved the way for molecular biology, gene therapy and personalized medicine. During his talk, Dr. Dove highlighted the basic principles of pathology—as related to infectious diseases—dating back to Robert Koch who proposed postulates to definitively prove cause and effect relationships between certain infectious agents and known diseases. He cited examples of brave investigators who self-experimented in efforts to expedite concepts that they were compelled to believe. Australia's Barry Marshall and Robin Warren received the 2005 Nobel Prize for *Physiology or Medicine* for their discovery of *Helicobacter pylori (H. pylori)* and its role in gastritis and peptic ulcers by isolating *H. pylori* from gastric ulcers and causing ulcers with the same bacterial species. These observations led to new treatments of gastric ulcers using combination antibiotic therapy. The contribution of microbial agents to diseases helps us find new etiologic factors for ongoing ailments including malignancies. Yet cause and effect relationships require highly compelling proof beyond presence of an agent in the diseased tissues. Bacteria and viruses have been isolated from a variety of lesions including cancerous tumors. Often, the challenge lies in determining beyond doubt whether the infectious agents appeared first causing the lesions or whether the lesions were susceptible to colonization by these agents.

My first talk on Saturday morning presented experimental evidence that circulating bacteria can colonize susceptible heart valves. The precise source of bacteria that may colonize a heart valve or prosthetic joint is difficult to identify. In fact, some publications have reported that many patients diagnosed with infective endocarditis (IE) do not have a history of valvular disease or other susceptibility factors suggesting that bacteremias with certain species of bacteria may cause valvular disease. Based on our studies at Loma Linda University, while the likelihood of colonization is directly related to the magnitude of bacteremias, even smaller levels of circulating bacteria can colonize a defective heart valve if the frequency of exposure is high. These findings provide evidence that bacteremias caused by physiological functions such as mastication, tooth brushing, or flossing can be a source of IE. Our experiments also showed that colonization of susceptible heart valves occurs within a week after a bacteremia event, also casting a shadow over cases that have implicated dental procedures that were performed months prior to IE diagnosis.

Dr. Sreenivas Koka introduced himself to AIOB seminarians by drawing on his diverse background of science and business acumen to urge us to question conventional wisdom and ask whether dogmas can be challenged and even simplified. One cannot help but use caution with accepted principles such as those proposed by Koch when these principles are interpreted rather than

strictly followed. For instance, less than 100 years ago, Westin Price attempted to prove that infected teeth cause many ailments including arthritis by selectively using some of Koch's postulates while disregarding the rest. He conducted experiments where he extracted teeth from human patients suffering from a certain ailment (Koch's first postulate: *The microorganism must be found in abundance in all organisms suffering from the disease but should not be found in healthy organisms*); he ignored the second postulate (*the microorganism must be isolated from a diseased organism and grown in pure culture*); he then implanted the extracted tooth under the dermis of rabbits and reported replication of the patient's symptoms in the animal (Koch's third postulate: *The cultured microorganism should cause disease when introduced into a healthy organism*); and lastly, he ignored the fourth postulate (*the microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent*). Based on his reports and those who read and interpreted his data, many patients were subjected to serial extraction of their teeth in efforts to resolve their disease conditions without any improvement.

Dr. Koka reminded us of the diligent process that Per-Ingvar Brånemark followed to develop the cylinder dental implants. The original success of this technology was safeguarded by the certification process that was required for clinicians to use the system. Brånemark made the certification process a requirement to ensure proper protocols were uniformly followed by all clinicians who used the implants. Outcomes derived from innovative technologies can be significantly impacted by variations in their application. Data in post-marketing studies may be different from the original controlled studies resulting in diminished outcomes or undesirable side effects. Evidence-based practices are promoted to employ rationale based on sound clinical data. Clinical studies are ranked based on study design with randomized clinical trials awarded the highest level. These types of studies are not always practical, and many procedures and techniques lack sufficient data to employ evidence-based practices. Many clinicians rely on their experience drawing on their own expertise and knowledge of practices that lead to lasting and predictable outcomes. Dr. Steve Traub presented cases with years of follow-up to illustrate the utility of immediate implant placement in extraction sites. In the real world where patients have busy schedules and prefer fewer visits to dental offices, practical approaches gain results that are satisfactory to clinicians and patients alike.

On Saturday, Dr. Dove used a well-known example of science fiction to illustrate how falsified publications can lead to lasting damage to the society. The impact of Andrew Wakefield's publications linking vaccination to autism continue to cause some parents to refuse vaccination protocols even years after retraction of the original paper. During the discussion session on Saturday morning, we were reminded of the fact that innovation is often slowly adopted while negative reports of existing standards of care are more rapidly accepted by many. Alexander Fleming's brilliant observation and discovery of penicillin in 1928 was not fully adopted as a means of combating infections until its full acceptance after WWII.

The new millennium promises improved outcomes based on personalized medicine replacing a shotgun approach or one-size-fits-all approach. Gene sequencing provides affordable and a real possibility to select patients who have the best chance to respond to a particular treatment or drug. Dr. Jennifer Grandis presented the challenges that we currently face with recurrent head and neck cancers. She also discussed her ongoing work at UCSF with newer approaches that can

lead to the discovery of more precise treatment of malignancies. Beyond their improved effectiveness based on new mechanisms of action, some of these product candidates show the promise of renewed responsiveness to existing drugs that have become ineffective due to resistance. Research is currently underway to use oncolytic viruses to prime patients who have undergone multiple rounds of chemotherapy so that they can more effectively respond to these agents.

Immunotherapy has gained significant traction during the past decade with the hopes to develop treatments that allow the body's own immune system to find and eradicate tumors. The 2018 Nobel Prize in *Physiology or Medicine* was awarded to James Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. These check-point inhibitors essentially remove the brakes from killer T lymphocytes to allow them to destroy cancer cells. While promising in theory, only a minority of patients currently respond to a single check-point inhibitor highlighting the importance of identifying responders from non-responders before initiation of treatment protocols. The lack of practical efficacy has led investigators to evaluate combination therapies to improve outcomes.

Immunotherapies are also gaining momentum in addressing the reverse problem where the body's immune system attacks normal tissues. In my talk, I reviewed Antigen-Specific Immunotherapies (ASI) for induction of tolerance to self and transplanted tissues. While these technologies are in early stages of development, ASIs have the potential to induce tolerance replacing current approaches of immune suppression or pathway blockers. Monoclonal antibodies (Mabs) have been used for the past couple of decades to block pathways involved in cancer development and inflammation with hopes to overcome more generalized immune suppression or chemotherapy adverse effects. Mabs have also encountered challenges with similar side effects such as increased susceptibility to infections and cancers, and loss of activity caused by development of neutralizing antibodies to the drug itself.

Dr. Dove reviewed the new and exciting field of gene editing technology designed to address genetic disorders. Gene therapy can be of great promise for diseases with known and inheritable traits such as hemophilia or cystic fibrosis. Like any technology, CRISPR/CAS9 is currently facing challenges in translation from preclinical to clinical applications as it moves from proof-of-concept in animals to clinical trials. The real challenge for this technology lies in the fact that the editing enzyme, CAS9, is derived from *Streptococcus pyogenes*, a bacterium to which most people have had previous exposure. Prior exposure is responsible for development of preformed antibodies, which diminish the effectiveness of products based on components of the bacterium. With any new innovation, challenges must be resolved to reach the desirable end goal.

On Sunday morning, our President, Dr. Ted Splaver, discussed the current evidence pertaining to the increased use of E-cigarettes. The initial allure for this substitute for traditional smoking was based on reduced deleterious effects and a means to replace or even cease smoking all together. New evidence suggests that whether wrapped in paper or used with an electronic device, smoking tobacco products continues to present health hazards. In fact, maintained constant blood levels of nicotine poses harmful effects with regards to healing independently of smoking. The debate on smoking tobacco and marijuana will continue for years to come. As legalization of marijuana continues with advocates touting its benign nature compared to currently legal products such as alcohol, the manifestations of this drug on the central nervous system are yet to be fully

elucidated. Perhaps we might take a detour from seeking expert advice from our oncology colleagues to include psychologists and psychiatrists who treat patients suffering from significant effects particularly with newer generation cannabis products and plant derivatives.

Oral and Maxillofacial Surgeons have always treated our victims of traumatic injuries caused by accidents or acts of war. In recent years, the battle ground has moved into urban areas. Dr. Alan Herford presented current efforts at one of the hospitals in our nation to prepare for these devastating events. Treatment and care provided to these patients requires multi-disciplinary training to manage the physical as well as psychological injuries to the victims and their families.

The 75th annual meeting of AIOB was a tremendous success because of the high caliber of presentations and the collegial exchanges in the lecture room as well as social events contributed by all AIOB members. The organizers truly care for the AIOB and look forward to seeing you all at the next meeting. I would like to thank Dr. Splaver for his leadership and Ms. June Barrientos for her tireless work to help organize the event throughout the year. I would also like to thank all members of the Board of Directors and Advisory Council for their contributions to the organization and annual meeting. Have a wonderful year and we look forward to seeing you in 2019.