Editorial

Advances and research in congenital heart disease

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The fate of babies born with congenital heart disease (CHD) has dramatically changed in the last 4–5 decades, going from a universally fatal condition in the vast majority of patients in the absence of diagnosis or intervention, to an entity whose outcome, at least in terms of peri-operative/hospital stay, has improved to an expected survival of about 96%. Indeed, since the first surgical solution for any type of congenital heart defect in 1938, ligation of a patent ductus arteriosus by Dr. Robert Gross at Boston Children's Hospital (1), followed by the pioneering work of Alfred Blalock and Helen Taussig in the palliation of "blue babies" with tetralogy of Fallot in 1944 (2), to the critical breakthrough of open heart surgery with inflow occlusion and repair of an atrial septal defect by F. John Lewis in 1952 (3), then the first operation done with the support of extracorporeal pump oxygenation by John Gibbon in 1953 (4), and cross-circulation championed by C. Walton Lillehei in 1954 (5), the field of surgical and interventional treatment and palliation for CHD has exploded into the success story we know today.

While these heroic pioneering surgical feats were necessary to break the ice, parallel developments such as cardiac catheterization and echocardiography in the 1950's needed 2 decades to mature and become clinical mainstream in the sixties to seventies, leading to further precision in diagnosis, real-time imaging, and follow-up of the heart. With the birth of pediatric critical care in the late seventies, improvements in cardiopulmonary bypass (CPB) perfusion hardware, the advent of percutaneous catheter-based cardiac interventions and refinements in anatomical and physiological understanding of single ventricle defects, the stage has been set since the 1980's for the current era of multidisciplinary treatment of CHD. Thus, guidelines and milestones have been established in the treatment of virtually every single congenital cardiovascular defect encountered in nature, ranging from near 100% survival and freedom from reintervention or repeat surgery for the more simple malformations, such as atrial or ventricular septal defects, patent ductus arteriosus and coarctation, to more complex defects with correspondingly lower peri-operative survival and the need for continuous follow-up and care.

Currently, in developed countries with established programs built with the sole responsibility to care for patients with congenital heart defects, surviving any given intervention or surgical procedure is really expected by caregivers and parents alike, but really comes to taking care of what CHD really represents, which is not a cure in most instances. Indeed, outcomes are no longer only measured by survival to discharge from the hospital, or even by freedom from complications which is of course an important measure of quality of care. Now that these immediate peri-operative goals are achieved in the vast majority of patients who go on not only to survive, but to grow up and become adolescents and then adults with treated CHD, the focus has shifted towards quality of life in the mid to long-term, developmental and learning processes, and a vast array of medical and social issues relating to what it means to live with "a treated heart condition". Tremendous technological feats at a macroscopic level which are obvious to the naked eye have already been achieved, are still being discovered, or being adapted and accordingly refined to help those patients already born and treated for CHD. More importantly, current and future focus are directed towards understanding the genesis, genetics, and corresponding earlier diagnosis with eventual new therapeutic strategies and targets at the fetal stage and/or even at the molecular level, for those

patients yet unborn.

What are some of the future directions which research could heavily influence? In many surgical repairs, from the newborn period to adulthood, somatic growth of the heart and vessels parallel to that of the patient must be taken into consideration. Prosthetic materials and implants are willingly avoided, with preference given to biological ones. While autologous tissue from the patient itself is the ideal material, having the advantages of being living tissue, thereby allowing for somatic growth, resisting infection, not requiring anticoagulation, and not inducing any rejection phenomenon, it is not always available in the appropriate amount or shape. The extant research and results of tissue engineering, using various combinations of biological scaffolds seeded with autologous stem or mature cells are most promising, but still have a ways to go. Although various living bio-engineered tissues have been produced and shown to function *in vitro* and *in vivo*, either in the myocardium, as valve substitutes, or as patch material, they have to date failed to endure the mechanical wear and tear of time, and therefore still need to stand the ultimate test of acceptable longevity. Furthermore, time constraints pertinent to harvesting cells from a given patient, treating and culturing them *in vitro* and seeding onto a scaffold which will eventually result in a functioning tissue ready for implantation back into the patient itself, make the current bio-engineered tissues unpractical, or definitely not a "real time" alternative. Ideally, such autologous bio-materials should instantly be "ready to use" in an off-the-shelf, custom-made, tailored-to-the-patient's-size manner, which will hopefully be achieved through technological advances in the near future.

In the field of neurological development, enhanced neuro-imaging modalities have allowed better documentation of the insults, injuries and malformations, or lack thereof, in neonates with CHD. Indeed, it is increasingly becoming apparent that in utero blood flow patterns specific to certain cardiac lesions which create a relative steal of blood flow away from the brain lead to significant cerebral lesions by birth, and therefore already exist prior to any surgical or interventional procedure on the heart. Although enhanced imaging and neuro-monitoring capabilities allow for better spatio-temporal documentation of what has already happened and how it may evolve in time with follow-up, more needs to be achieved in understanding exactly what processes lead to the neurological insults, and more importantly, what can eventually be done to influence the course of events, or more ideally, even prevent any harm in the first place. Huge research efforts are still needed to fully identify, understand and hopefully influence the patho-physiology of neurological injury and capacity for repair/regeneration in the heart-brain axis of patients with CHD.

As the various intricate and delicate stages of embryogenesis of the heart are better defined and understood, so also has advanced the bold strategy to intervene and hopefully influence certain critical key structures and blood flow patterns in the developing heart. Intrauterine intervention, either by percutaneous/trans-uteral catheter balloon dilatation or by open surgical technique, has been successfully performed, most notably on the aortic valve, in fetuses with aortic valve stenosis, hypoplasia or atresia and variants of hypoplastic left heart syndrome (6). The risk-benefit ratio should take into consideration treating two patients, the mother and the fetus, since both of the patients could potentially suffer, and only one (the fetus) benefits. Whether in-utero treatment techniques can reliably result in favour of both mother and fetus remains to be demonstrated, which is why only a few highly specialized centers are undertaking it with promising results (6).

Although major advances have been made in the field of genetics with regards to diagnosis which then influences prognosis and genetic counselling, the vast majority of the etiology of congenital heart defects remains incompletely understood or unknown (7). Roughly 30% of CHD patients have phenotypes which fit into syndromes including extracardiac manifestations. That leaves about 70% of cases in which no syndrome exists, and for whom only some have known Mendelian inheritance (dominant or recessive). This leaves a lot of room for the interplay of multifactorial etiologies such as the interactions between multiple genes, environmental factors, and spontaneous mutations, just to name a few. Therefore, currently, there is still a time-lag between the objectives of genetical testing in clinical practice with a goal to assist in diagnosis, help define prognosis and aid in parent counselling, or their value for research purposes which may lead to insights into a disease entity and potential future therapeutics targets. The future interplay between clinicians and research laboratories to bring together patterns of knowledge that fit will be of paramount value and provide additional keys to the understanding of the genesis/genetics of CHD.

In conclusion, the field of care for congenital heart defects has made tremendous strides in its young infancy. In no other field of science or medicine has so much been accomplished in so little time, with heart defects that were an unconditional death sentence 60 years ago, to

the current operative survival rates of more than 96% for all defects considered together. We must give tribute to bold pioneers in the early days of the 1940's and 1950's for taking the biggest steps, with further refinements in the 1970's and 1980's to reach the point where we are today. However, for certain defects, we are only scratching the surface, and short-term as well as long-term outcomes are still unsatisfactory. Owing to huge advances in perinatal care, increasingly premature babies with complex syndromes involving multiple organs are no longer subject to "natural selection" and are surviving, bringing with them an array of cardiac and associated non-cardiac malformations that confound not only cardio-pulmonary physiology, but require a more holistic approach to patient care. Furthermore, although surviving an operation or intervention for a congenital heart condition is now expected for the vast majority of patients as neonates and infants, the focus is shifting towards quality of life, long-term issues, and treatment/care algorithms for adults having survived their initial hurdles, who now represent the majority of patients with CHD, a new fast-growing population. Much collaboration, vision and innovation is still needed to tackle and understand congenital heart defects, giving providers who are privileged to be involved in the care of these patients and families challenges for many decades to come.

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Footnote

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