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The Five Greatest Discoveries During the Evolution of Perfusion

Introduction

The history and evolution of perfusion is well documented. Numerous textbooks chronicle the advances in extracorporeal circulation over the last 100 years quite eloquently. Ideas, techniques, and equipment once thought to be "state of the art" are continually cast aside in lieu of new developments and research findings. And yet, like a vintage car or classic movie, some discoveries are timeless and stand out amongst the rest. To be revolutionary, a discovery must change fundamentally or completely what is considered the status quo. It's fortunate, then, that changes in perfusion practice have occurred largely with an eye towards skepticism.

Perfusionists, after all, are gadgeteers and tinkerers at heart. We are slow to accept and quick to scrutinize. We don't mind change, but it must come at a slow, purposeful, and methodical pace. Sticking to the fundamentals is surely an attribute to be proud of, and it has kept the perfusion profession on a conservative course of success. Likewise, we're eager to embrace the many discoveries that have changed for the better the way we deliver patient care. Five discoveries, in particular, stand out as revolutionary.

1. Heparin

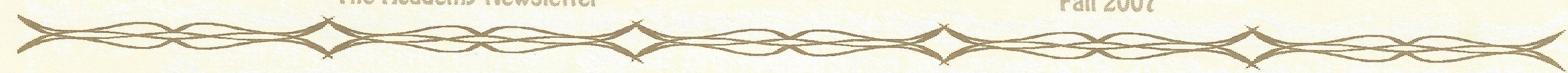
Heparin was discovered by Jay McLean in 1916 at Johns Hopkins University in Baltimore. Beginning in 1918, Howell and Holt published a series of articles describing heparin's chemical structure, as well as the need for purification and standardized dosing of this crude extract.

Heparin, in a form clinically safe for humans, however, would elude researchers for another twenty years. In 1929, Dr. Charles Best at the University of Toronto began studying heparin because he observed that "no anticoagulant was safe for clinical work and none was being used". In 1933, Dr. Gordon Murray, a vascular surgeon at Toronto General Hospital, joined Dr. Best's research team. Within two years, Best, Murray, and colleagues had produced a form of heparin safe for human use. On April 16, 1935, Murray administered heparin for the first time to a patient with deep vein thrombosis at Toronto General Hospital. Heparin became commercially available in 1937 as an extract of beef liver. In the ensuing years, heparin was purified from bovine lungs and porcine intestines as well. Today, the heparin extraction process utilized by pharmaceutical manufacturers is virtually the same as that first described by Best in the 1930s.

Interestingly, Gibbon obtained heparin from the University of Toronto for his 1934-1935 animal experiments. At the time, many researchers worried that fatal hemorrhage would result given the large doses of heparin routinely administered by Gibbon (e.g., 60 mg of heparin in a 3 kg cat). These early heparin preparations, however, were weak in strength (15 units of activity per mg). In addition, Gibbon's experience with protamine dosing and his meticulous attention to hemostasis virtually eliminated this danger.

2. Azygous "Low Flow" Principle

From the earliest days of perfusion, the generally accepted minimum arterial flow needed to sustain life (at normothermia) was 100 to 165 mL/kg/min in both animals and man. This belief that arterial flow must equal basal cardiac output was logically sound. But all too often the surgical field would be flooded with blood, making visibility for the surgeon nearly impossible. Furthermore, flow rates of this magnitude overwhelmed the oxygenator's then limited capacity, and irreparably damaged the blood. Then in 1952, an article appeared in a British periodical that caught Dr. Walt Lillehei's attention. The article, published by Andreason and Watson, reported that dogs tolerated prolonged periods of inflow occlusion at normothermia provided blood flow from the azygous vein was allowed to enter the heart. Lillehei's group, including Dr. Morley Cohen, used dogs to further quantify this remarkable observation, and determined that the azygous flow was around 70 to 80 mL per minute. Next, the measured azygous flow was plotted against the dog's body weight. On average, the flow was determined to be between 8 and 14 mL/kg/min. The implications of the azygous flow principle were staggering. After all, survival following such a low flow state refuted the fundamental assumption that to avoid organ damage blood flow must equal basal cardiac output. And yet, Lillehei's experiments clearly showed that dogs could survive provided the "azygous" low flow period was kept at 35 minutes or less. This principle, that



only 10% of the total cardiac output was needed to sustain life, was monumental in making cardiopulmonary bypass an eventual reality.

3. Turbulence

In 1915, Richards and Drinker described an apparatus for the perfusion of isolated organs. Their description included turbulent flow as a means of improving blood oxygenation. Turbulence, of course, is closely related to hemolysis, and their keen observation went largely unnoticed for over 30 years. Dr. Clarence Dennis, the first surgeon to attempt cardiac surgery with the aid of cardiopulmonary bypass in 1951, once remarked that Gibbon's revolving cylinder was the best method ever devised for oxygenating blood. True, perhaps, but the cylinder lacked surface area and therefore, efficiency. So much so, in fact, that Gibbon himself estimated that a cylinder at least two stories high would be needed to support an adult human. Fortunately, Dr. Thomas L. Stokes, Jr., and Dr. John B. Flick, Jr., both members of Gibbon's research team, made a highly significant observation. Like their predecessors Richards and Drinker, they observed that turbulence improved blood oxygenation. This led to the implementation of a wire screen lining inside the revolving cylinder. Further refinements included the use of plastic mesh or perforated

steel plates, each offering varying degrees of improvement. Stokes and Flick published their findings in 1950.

Turbulence (the very word sounds destructive), and the enhanced oxygenation that it afforded, enabled Gibbon to abandon his cylinder-type oxygenator in favor of the stationary screen-type model. Engineers from IBM were called upon to mathematically determine the optimum screen area and configuration needed to maximize oxygenation and minimize hemolysis and foaming. In time, the word 'turbulence' would give way to phrases such as "secondary flow vortices" or "disruption of the boundary layer". The use of turbulence in oxygenator design might well have reached its zenith when Johnson & Johnson introduced the Extracorporeal Interpulse membrane oxygenator in the early 1980s. The system included a large cumbersome piece of hardware called a 'pulsator' which violently shook the membrane in order to disrupt the boundary layer of the blood path. Perfusionists of the day affectionately referred to this device as the "shake and bake".

4. Hemodilution

Early researchers insisted that extracorporeal circuits be primed with fresh, anticoagulated, homologous whole blood. Heparin was the generally-accepted anticoagulant, although blood stored in solutions containing citrate and dextrose was proven safe for extracorporeal circulation around 1960. The demand for fresh homologous blood led to an immediate strain on the blood blanks, and many open-heart surgeries of the day were either delayed or postponed for lack of correct type or amount. In addition, there appeared certain intraoperative problems that occurred when a blood prime was used. As cardiopulmonary bypass commenced, a pre-

cipitous fall in both arterial pressure and venous return was observed. This shock-like state resulted in metabolic acidosis, thrombocytopenia, leucopenia, and pulmonary congestion. Gadboys, Slonim, and Litwak determined in 1962 that an incompatibility between patient and the blood units was at fault. Furthermore, there was most certainly an incompatibility between the individual pooled blood units. They termed this combination of sequelae the 'homologous blood syndrome'. In 1959, Panico and Neptune designed a pump oxygenator that utilized normal saline as its priming agent. Shortly thereafter, Zuhdi and colleagues reported use of a priming agent comprised of 5% dextrose in water. Cooley's group in Texas further popularized the use of non-hemic priming agents, as did Lillehei's group in Minnesota. The use of a non-hemic prime solution allows easy accommodation of emergency procedures, and has permitted cardiac operations in thousands of members of the Jehovah's Witness faith.

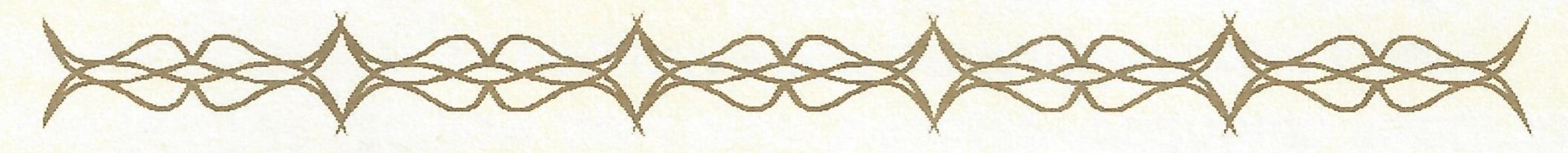
5. Hypothermia

Man's intriguewith cold and hypothermia stems backward for many centuries. James Currie may well be credited with first applying cold for medicinal purposes around the close of the 18th century. Using a thermometer devised by the renowned surgeon John Hunter, Currie studied cooling as a means to treat fever, seizures, and even mental disorders. During the 19th century, French, German, and Russian physiologists alike used hypothermia to study bodily functions. It was established at this time, for instance, that hibernators could be cooled to near freezing and survive, yet nonhibernators such as rodents would succumb to temperatures around 18 degrees Celsius. In the early 1900s, Temple Fay and colleagues in Philadelphia tried lowering the temperature of advanced cancer patients. Although their studies added to the understanding of the body's reaction to cold, the cancer persisted. With respect to the application of hypothermia in open-heart surgery, Dr. William Bigelow is the undisputed champion. In 1941, as a surgical resident at Toronto General Hospital, Bigelow amputated the fingers of a young man suffering from frostbite. Following four years of service in the Canadian army, Bigelow spent a year at

Johns Hopkins University with Dr. Alfred Blalock. Stimulated by the fresh knowledge, ongoing research, and brilliant minds at Johns Hopkins, Bigelow awoke one night with a simple solution: "Cool the whole body, reduce the oxygen requirements, interrupt the circulation, and open the heart". Upon returning to Toronto in 1946, Bigelow set up a lab and began experimenting with dogs, woodchucks, and even monkeys. In September of 1952, Dr. F. John Lewis of Minneapolis performed the first successful open-heart surgery (ASD closure) using hypothermia and inflow occlusion as described by Bigelow. By early 1953, Henry Swan and colleagues in Denver reported successfully correcting pulmonary valve stenosis in numerous children using Bigelow's techniques. From the mid-1950s to the late 1960s, the surgical literature was flooded with articles about hypothermia. The prospect

Ventricular Assist Device Resource Center

A new website dedicated to ventricular assist devices is now available. www.vadrc.com is the Ventricular Assist Device Resource Center. This site is designed to provide a central location for access to troubleshooting alarms, educational materials, operator manuals, instructional videos, meeting information, discussion forums and more for many types of VADs and TAHs. While you are at the site please visit and register in the forum. Communication between those who utilize VADs in a forum setting can be invaluable for sharing information and techniques in this rapidly growing area of our profession.



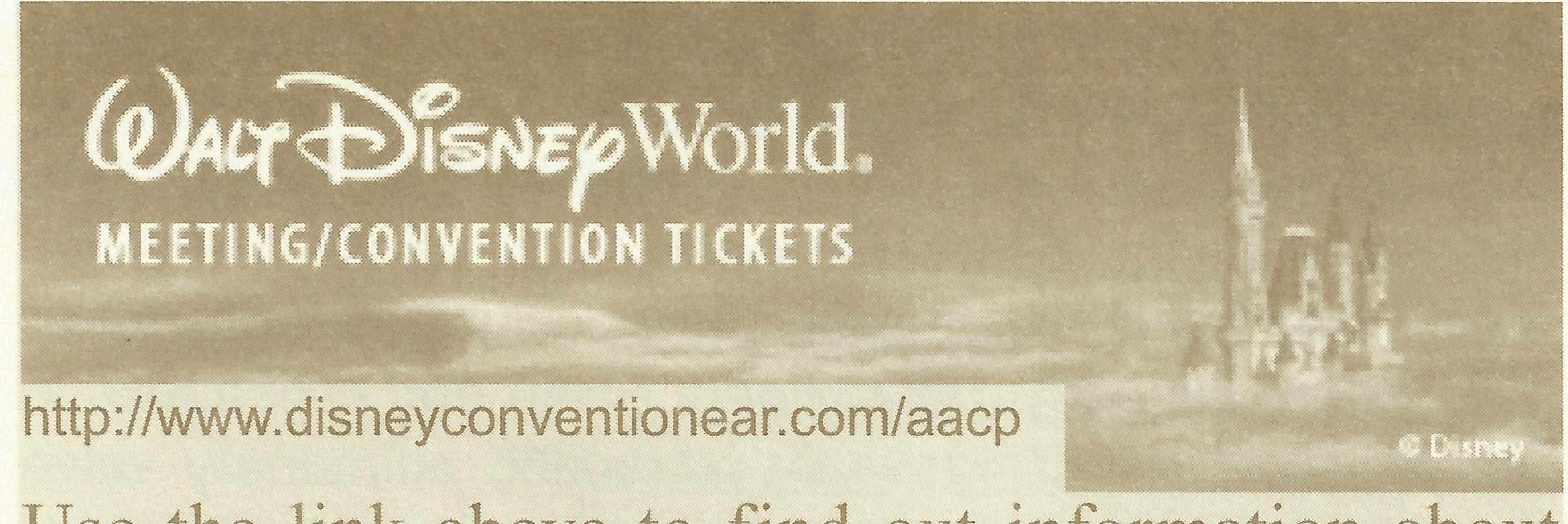
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that hypothermia will forever be a favorable adjunct to heart surgery appears likely.

Conclusion

Over the years, advances in oxygenator design and blood propulsion techniques have made cardiopulmonary bypass safe and effective. Certainly then, DeBakey's application of the roller pump to heart surgery should be considered monumental, if not revolutionary. The same applies to Kolff's early research in membrane oxygenation, Melrose's use of cardioplegia, or perhaps Latham's design of a centrifugal bowl for blood separation and processing. Standing the test of time was not a deciding factor in choosing the five greatest discoveries. Rather, it seemed appropriate to list the discoveries that were, for lack of a better word, underrated. And so, in pump rooms across this country and elsewhere ... let the debate begin.

Author's Note: A full list of references that form the basis of this article is available upon request.



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Contact email: agm@cscp.ca

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