Matters @ Heart

An odyssey in science and medicine

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Tales from the past, when told to a new generation, create little interest, particularly when they recount personal events only. However, when they deal with flesh and blood men and women, and of the eddies in the stream of time, they hold our attention. A look in the past can reveal the origin of ideas and relate them to the men and women who created them. This tale is an attempt to recount developments in medical science as personally experienced during the last seventy years. I hope this will show that science is a child of its time bound to thoughts and technology of its time. Therefore, we should not apply today's standards to the work that came before us.

In 1935, a year after I had obtained my MD degree, I was a research fellow at the Carlsberg Biological Institute in Copenhagen, Denmark, which was financed by the Carlsberg Brewery. The institute was built primarily for the study of cell cultures. The director of the Institute was Albert Fischer, a student of Alexis Carrel from the Rockefeller Institute, now the Rockefeller University in New York City. What was tissue culture like in the early part of the 20th century? I had been exposed to this technique in the early 1930s as a medical student in Berlin, volunteering for Rhoda Erdman, a pioneer in the field of tissue cultures. In 1907, Ross Granville Harrison, when at Johns Hopkins Hospital, was the first to devise a method to grow tissue fragments outside the body. He not only initiated this technique, but also was able to show that nerve fibers develop from particular nerve cells in the brain and the spinal cord. Harrison placed the tissue derived from a frog on a cover slip, inverted it over a hollow ground microscope slide, and sealed it with paraffin. When Harrison was proposed for the Nobel Prize for a second time, the committee eliminated him because "of the rather limited value of the method and the age of the discovery." In my early Hopkins days in 1943 my laboratory at Johns Hopkins Hospital was close to that of George Otto Gey, who, using his roller tube technique, propagated cells, viruses and malignant cells in vitro for long periods of time. Gey is remembered particularly for his growth of malignant He-La cells in cell cultures. The word He-La is an abbreviation of the name of a young woman with cervical cancer whose tissue was cultured. Gey was a tall outgoing man who always welcomed young investigators to his

The Carlsberg Biological Institute in Copenhagen, where the author started on his odyssey. Courtesy of Carlsberg A/S.

Demonstration of nerve fiber growth in an experiment by Ross Granville Harrison, in 1908, showing two views of the same nerve fiber, taken 50 minutes apart, during which time the fiber has stretched. © Wellcome Images.

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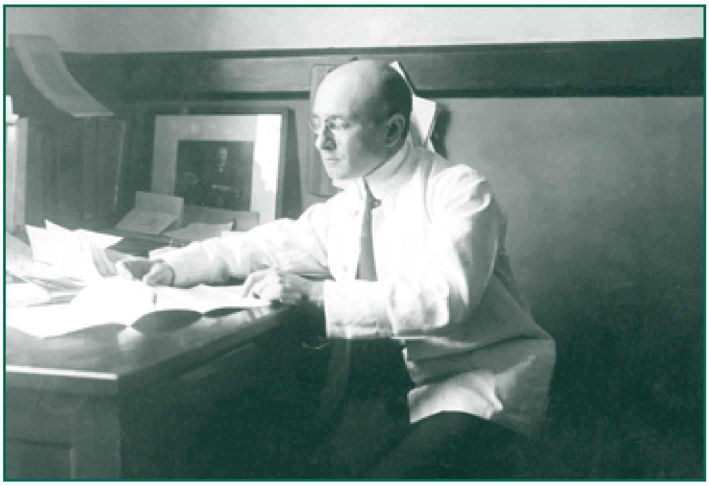
lab. Harrison's experiments attracted the attention of Alexis Carrel. In 1909, Carrel sent his assistant Montrose T. Burrows to Harrison to learn the method and adapt them to the tissues of warm-blooded animals. Carrel introduced sterile technique and the Carrel flask, which could accommodate more tissue and medium. This led to the development of synthetic and defined media. In 1913, Conti in France introduced the time-lapse camera, which showed migrating and dividing cells. Today's tissue culture has become an essential tool in the growth of viruses, of cancer cells, and the study of biology of tissue.



French surgeon and biologist Alexis Carrel (Nobel Prize in Physiology or Medicine in 1912) working at his desk. © Bettman/CORBIS.

He-La cells stained with Hoechst 33258. Inset: Henrietta Lacks, in the mid-1940s, from whom the immortal He-La cell line was obtained and after whom it was named. All rights reserved.

In 1937, I received a Rockefeller fellowship to work at the Rockefeller Institute in New York with Alexis Carrel. Carrel was born in France and received the Nobel Prize for his work on organ transplantation; he also contributed to the development of cell culture. He was an unusual scientist who believed in parapsychology; but he was an inspired innovator, a scintillating personality whose interests in nonscientific matters did not endear him to the staff at the Rockefeller Institute. He made the vital mistake of returning to France when the Nazis occupied it, in the vain hope of helping his beleaguered country. To me, Carrel was a great teacher and a friend. Among the scientists at the Rockefeller Institute were Oswald Avery, Peyton Rous and Karl Landsteiner. I had the opportunity to talk to members of their department, the contact facilitated by a faculty dining room, presided over by a painting of Lavoisier and his young wife. Landsteiner had received the Nobel Prize for his discovery of blood groups. He was one of those scientists who liked to work at the bench, trusting only results which he himself had personally obtained. A simple experimental arrangement led to his discovery of blood groups. As he wrote in his Nobel lecture from 1930, "my experiments consisted of causing the blood serum and erythrocytes of different human subjects to react with one another." He concluded that "it became clear that the reactions follow a pattern which is valid for the blood of all humans, and that the peculiarities discovered are just as characteristic of the individual as are the serological features peculiar to an animal species. Basically, in fact, there are four different types of human blood, the so-called blood groups. The number of the groups follows from the fact that the erythrocytes evidently contain substances with two different structures, of which both may be absent, or one or both present in the erythrocytes of a person." His discovery made the use of blood transfusions possible.

Antoine-Laurent Lavoisier (1743-1794) and his wife Marie-Anne-Pierrette Paulze, also a chemist. Painting by Jacques Louis David. © Metropolitan Museum of Art, dist. RMN.

Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe.

[Aus dem pathol.-anat. Univ.-Institute des Prof. Weichselbaum in Wien.]

Von Dr. Karl Landsteiner in Wien.

I. Zur Serumdiagnostik der Fermente.

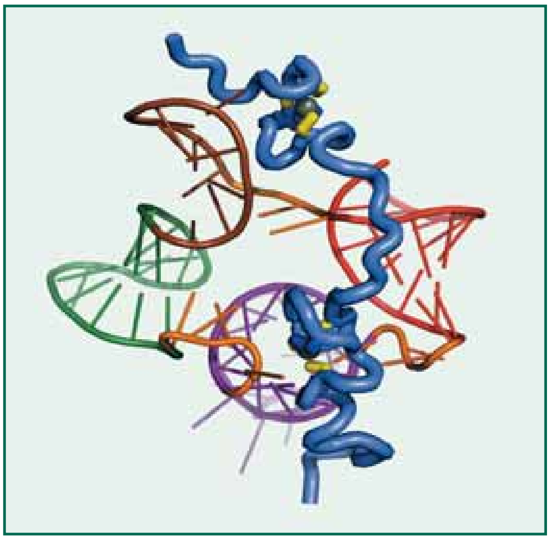
Karl Landsteiner's groundbreaking 1900 publication describing the agglutinating properties of blood sera, which was to lead to the discovery of the ABO blood group classification system. © Wellcome Images.

Another Nobel Prize winner at the Institute was Peyton Rous. I found him always willing to talk about his work. He had been for many years the editor of the *Journal of Experimental Medicine,* and was a strict judge. He even edited the famous paper by Avery on the transformation of pneumococci, but it is questionable whether this great contribution needed his editorial work. He received the Nobel Prize in 1966, when he was over 80, for the discovery of a virus which produces tumor in chickens. Rous in 1910 "described a malignant chicken sarcoma which could be propagated by transplanting its cells, these multiplying in their new hosts and forming new tumors of the same sort." He mentioned that "its cells yielded a causative virus." It is now recognized that cancer is the result of many genetic mutations and dysregulations of cellular pathways, which lead to the formation of new blood vessels through angiogenesis. In solid tumors, the cells form a wide variety of signaling systems, which include angiogenic factors. Viruses are just some of the myriad of factors which can lead to dysregulation. The search goes on!

The third in this constellation at the Rockefeller Institute was Oswald Avery. He never did receive the Nobel Prize, although he richly deserved it. A Canadian by birth, he received his MD from the College of Physicians and Surgeons of Columbia University. He became interested in the factor which transforms rough into smooth pneumococci; Avery demonstrated that DNA and not proteins is responsible for the transformation into the genetic machinery of the rough cells.

After a surgical internship at the College of Physicians and Surgeons of Columbia University under A. O. Whipple, the initiator of the Whipple procedure for carcinoma of the pancreas, I joined the department of physiology at New York University under Homer W. Smith whose scientific interest was renal physiology. Smith was also a great writer, a novelist who had the gift to express his ideas on evolution with originality and style. In renal physiology Smith used the concept of clearance introduced by Rehberg and van Slyke. Biochemistry had not made inroads into renal physiology. At Bellevue, Homer W. Smith was the center of the group working on the role of the kidney in hypertension and shock, and Dickinson Richards and André Cournand began their work on catheterization of the heart, primarily interested in pulmonary circulation. Cournand was a careful and systematic worker, while Richards was interested in the grand design. He was a humanitarian and a scholar, a highly cultured New Englander and an all-round scholar. Cardiology at that time was primarily concerned with flow and pressure, and right heart catheterization was an ideal tool to study these new parameters.

During World War II, I spent time in the medical corps and the chemical warfare division of the US Army. I later joined the department of Surgery at Johns Hopkins Hospital under Alfred Blalock, to work on congenital heart disease. It was an exciting time. Cardiac surgery was in its early stages and Blalock had just published his early results on the surgery of congenital heart disease. This gave us the opportunity to define, by means of right heart catheterization and other physiological tests, the circulatory changes in these disorders. Open-heart surgery was still in the future; therefore Blalock's technique was limited to conditions that could be treated by methods that



Structure of Rous sarcoma virus (RSV) nucleocapsid protein NCp12 bound to the cognate muPsi RNA packaging signal.

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Alfred Blalock (on far side of the table) with Vivien Thomas, his senior laboratory technician, close behind him, performing a shunt procedure on a 9-year-old girl with tetralogy of Fallot. © Johns Hopkins University and Johns Hop-kins Health System.

avoided direct surgery on the heart itself. The work on congenital heart disease was carried out with a group of brilliant young surgeons.

At that time, we noticed that catheterization of the coronary sinus in man could be carried out at will. From then on our work was primarily concerned with the extraction and utilization of foodstuffs by the human heart and their contribution to its oxidative metabolism. We continued this work at the University of Alabama in Birmingham and found that the heart was, as Taegtmeyer expressed it, "an organ with metabolic flexibility." It uses carbohydrates, fats, and amino acids according to their availability, and myocardial failure is not accompanied by changes in myocardial extraction of foodstuffs. We began to recognize that the heart is a metabolic organ rather than a mere pump, which regulates and is regulated by flow and pressure. Alabama was followed by Washington University in St Louis, by Wayne State University in Detroit, and finally by the Huntington Medical Research Institute in Pasadena. In Detroit we introduced coincidence counting in the determination of human coronary flow in situ.

I hope this incomplete tale has brought out some general facts about the progress of clinical and fundamental research. Yesterday's research looks primitive and simple as compared to the present. But I would venture that our successors 50 years from now will look at today's research with the same degree of condescension that we reserve for the work of our predecessors. Science and art are the children of the times during which they are created. The style of creation changes, but human nature changes little. There also should be close dialogue between research carried out at the bench and at the bedside. Research should, like Claude Lenfant expressed it, "gather from the tree of knowledge fruit for the solace and refreshment of mankind."

"Tree of Knowledge" illustrating Arbor Scientiae, *a medical treatise by Ramon Lull (1232-1315). All rights reserved.*

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