Beyond Influenza: More Centrifuge-based Oak Ridge Medical Instrumentation

(As published in The Oak Ridger's Historically Speaking column the week of February 12, 2018)

Al Ekkebus wrote *A better life through centrifuges,* and now he follows up with additional details.
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After the recent article on centrifuge use for purifying vaccine appeared in the October 25, 2017, *Oak Ridger's*, *Historically Speaking* column, an insightful reader (Gordon Fee) expressed interest in learning more details about other technologies that were commercialized relating to vaccines, blood analysis, or cancer research or treatment.

Perhaps the most famous technology developed in Oak Ridge for cancer treatment involves radioisotopes. Nuclear medicine began in the 1930s with the experimental use of radioisotopes to treat lymphomas and other diseases. The American Chemical Society named Oak Ridge National Laboratory a National Historic Chemical Landmark in 2008 for the Production and Distribution of Radioisotopes.

On June 14, 1946, Clinton Laboratories (predecessor in name to ORNL) published a catalog in *Science* magazine. The catalog consisted of reactor-produced isotopes that Clinton Laboratories could prepare and distribute for scientific and medical uses.

Less than two months later, on August 2, 1946, Eugene Wigner, standing in front of the Graphite Reactor, presented a small container of Carbon-14 to the director of the Barnard Free Skin and Cancer Hospital of St. Louis. Less than a year after the conclusion of World War II, this marked the change of direction of the Manhattan Project from wartime to civilian purposes.

It was estimated that by 1950, the number of radioisotope shipments from the Graphite Reactor neared 20,000. The shipments continued through the years and even today ORNL remains a primary source of radioisotopes.

Interest by physicians also grew. As of July 31, 1964, there were 1,085 physicians in the United States licensed to use radioisotopes in private practice. There were also some 1,201 medical institutions licensed to handle radioisotopes.

After the closing of the Graphite Reactor in 1963, radioisotope production shifted to the Oak Ridge Research Reactor and then to the High Flux Isotope Reactor, which continues that tradition today for those isotopes not available from the commercial sector.

The previous article described use of the centrifuge to purify influenza vaccines. *The Tennessean* headline on October 24, 1967 shouted "Pure Vaccine for Flu Ready," in which Eli Lilly's director of research said his firm has been licensed by the government and has available a pure flu vaccine with greatly diminished side effects and reactions.

At about this time, the rabies vaccine was also targeted locally for purification. In 1969 at a National Research Council meeting, ORNL's Norman Anderson, noted that a new centrifuge rotor has been used to isolate high-purity rabies virus. He said this joint effort between Eli Lilly and ORNL demonstrates the feasibility of preparing a pure rabies-virus vaccine.

These vaccine purification efforts using centrifuges were significant, but there was another technology developed locally, under the leadership of Norman Anderson, that focused on a technology useful to specific individuals — the centrifugal fast analyzer.

As part of the Molecular Anatomy (MAN) Program at Oak Ridge Gaseous Diffusion Plant, Norman Anderson and his team from ORNL's Biology Division also invented the first centrifugal fast analyzer. It was named GeMSAEC in honor the agencies that funded its development (National Institute of General Medical Sciences and the Atomic Energy Commission).

This instrument performs chemistry tests on multiple samples of blood or other bodily fluids simultaneously. It is built around a rotor and measured quantities of the samples and reagents are introduced into individual wells toward the center of the rotor.

When rotating, samples and reagent are mixed and moved into transparent cells at the outside of the rotor. During each revolution, measurements are made of a physical property such as light transmission, color, or fluorescence.

The course of the chemical changes in each reaction cell is monitored by an online computer, and analytical results are developed simultaneously for all samples on the rotor. The resulting data are stored, interpreted, and results are provided quickly; one run of the analyzer can perform the same analysis on up to several dozen samples. The centrifugal fast analyzer was included in a 1986 Department of Energy Report summarizing accomplishments of DOE and its national laboratories in health and environment over the previous 40 years.

Anderson later recalled that during a dinner by himself he used a blank space in a Washington Post ad to sketch his idea for a rotor for the device that would enable the analyzer to be self-cleaning. After dinner, he inadvertently threw the newspaper away but later remembered enough detail to continue development the next day.

The centrifugal fast analyzer was named an Industrial Research Magazine IR-100 Award winner in 1969 as one of the 100 most significant new technological products. Licenses for this model were granted to American Instrument Co., Electro-Nucleonics, Inc.(ENI), and the Union Carbide Corporation. A 1978 *ORNL Review* article notes that the annual sales of centrifugal fast analyzers are over $50 million annually with the ENI market alone extending to Russia, Japan, Czechoslovakia, and England.

The centrifugal fast analyzers brought true automation to clinical chemistry (as differentiated from mechanization). Data generated in the testing was converted to meaningful information with the use of an online computer that was part of the analyzer.

Major markets for the centrifugal fast analyzer are small-to-moderate-sized hospitals, and specialty laboratories in large hospitals. This enabled a significant reduction in time between testing and availability of results.

Major advantages of the centrifugal fast analyzer are its throughput capacity, flexibility to perform any type of assay, the ability to economically perform single tests, all of which are valuable in an emergency. At the time of its introduction, the centrifugal fast analyzer represented a 25 to 50 percent cost savings over the discrete analyzers then available.

All of this resulted in considerable cost savings to users, particularly in the area of reagent costs, of 10 to 30 cents/test performed on centrifugal fast analyzers. For the 300 million tests/year, this means annual estimated savings of $30 to $90 million.

NASA began funding a miniaturized version (zero gravity) of the analyzer for use in SKYLAB B. Although this mission never flew, several portable versions were built and tested at Johnson Space Center, ORNL Health Division, NIH, and Albert Einstein Hospital, with funding provided by EPA, Food and Drug Administration, and the AEC. A third-generation miniaturized unit was developed which featured an on-board integrated computer and portability; in 1977, it too was named an IR-100 Award winner.

In 1969, the centrifugal fast analyzer program moved to the ORNL site and the Chemical Technology Division with leaders Chuck Scott and Carl Burtis. This work formed the basis for development of a blood rotor by ORNL staff Carl Burtis, Wayne Johnson, and William Walker. Abaxis Corporation licensed this product in 1993. The blood rotor was a miniaturized and computerized version of the centrifugal analyzer that contains chemical agents and processing chambers needed to automatically process and analyze a sing drop of blood.

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I thank Ray Smith and Gordon Fee for encouraging my hunt for information. I was aware of some of these developments, I was not aware of their genealogy until I investigated this article.

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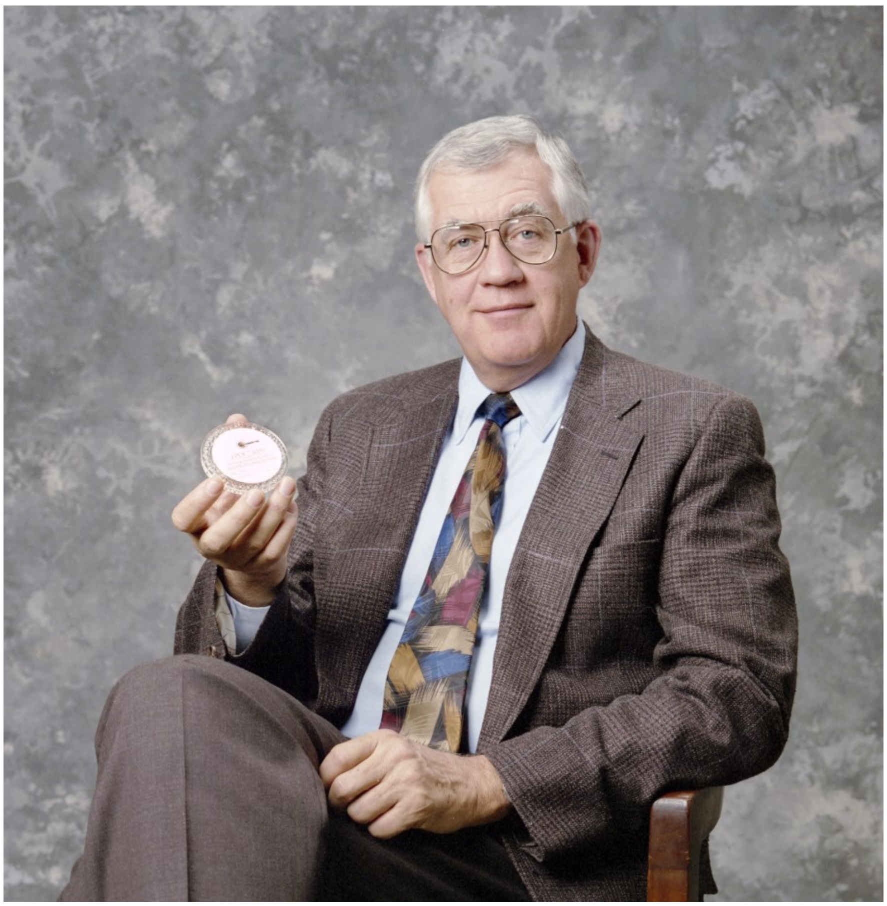
Thanks Al, for even more insight into the valuable research and development of significant technology and the various uses being implemented. Oak Ridge inventions have, since the beginning in the 1940s continued to benefit the world in many ways.

I wish for a comprehensive listing of all the significant technological advances coming from Oak Ridge! I believe we would all be amazed at the length of such a list and the wide variety of things we now take for granted which were first thought of and developed in Oak Ridge!



Carl Burtis shows the Abaxis disposable rotor used to monitor patient health

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Eugene Wigner hands off the Carbon 14 radioisotope shipment, first radioisotope shipment of many through the years