Celebration of the 10th anniversary
Caudwell Xtreme Everest Expedition
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The Invention and Development of Blood Gas Analysis

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Background: In 1952, after 6 months of anesthesia residency and a year of research in respiratory physiology at Penn, the doctor draft caught me. I entered the US public health service and was placed in the new anesthesia department of the NIH Clinical Center Hospital in Bethesda. Cardiac and brain surgery required hypothermic blood gas analysis. That required changing the Henderson Hasselbalch equation constants as functions of patient temperature. This drove me into electrochemistry.

History of ionic and electrometric chemistry

Michael Faraday (1791-1867)

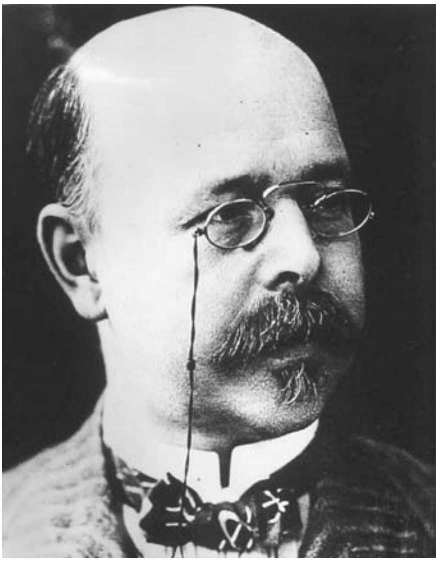
Faraday was an English scientist who contributed to the study of electromagnetism and electro-chemistry. His main discoveries include the principles underlying electro-magnetic induction, diamagnetism and electrolysis. Although Faraday received little formal education, he was one of the most influential scientists in history. He discovered the laws of electrolysis. It was largely due to his efforts that electricity became practical for use in technology.

Svante Arrhenius (1859-1927)

In his thesis at age 25, Arrhenius was the first to prove that salts in water separated into ions. That idea was proposed by Michael Faraday 50 years earlier but no one had proved it. Arrhenius' thesis data showed that conductivity increased less than predicted as salt concentration was increased. His thesis was disbelieved and at first rejected by Uppsala professor Per Cleve, and though Arrhenius revised his dissertation and won the support of a famous Latvian chemist, Wilhelm Ostwald, Cleve gave him the lowest possible passing grade. Arrhenius was awarded the Nobel Prize in 1903. Cleve was invited to explain the award. Arrhenius soon became the director of the Nobel Institute and won recognition as an expert physicist, chemist, physical chemist, geologist and geochemist. A century ahead of time, he predicted global warming from rising atmospheric CO_2 in 1896.

Wilhelm Ostwald (1853-1932)

Walther Nernst (1864-1941)



Wilhelm Ostwald in Riga Latvia went to Uppsala to argue for Arrhenius' ionic theory. He later used it to measure acid strength with a platinum electrode in a hydrogen saturated bath in 1890. This was useless for blood because all the CO_2 escaped. Ostwald got a Nobel Prize in 1909 for electrochemical theory and discovery. Ostwald's student, Walther Nernst, applied the well-known gas laws to Arrhenius' ions. He wrote the electrical equation determining the potential between two salt concentrations. He has been called the father of electrochemistry. Nernst won the Nobel Prize in 1920.

Søren P.L. Sørensen (1868-1939)

In 1907, Sørensen simplified the hydrogen ion nomenclature by defining pH as the negative log of H^+ ion molar concentration. pH of 7.0 replaced writing a concentration of 0.0000001 Moles/L.

Lawrence J. Henderson (1878-1942)

He was Professor of Biochemistry and Physiology at Harvard. In 1905-7 he was the first to understand the complex relationship between bicarbonate ion, hydrogen ion and PCO_2 He introduced the term "buffer" and the idea of buffering. He wrote what has come to be called the Henderson equation. It doesn't make sense to me because it didn't use pH.

Karl Hasselbalch (1874-1962)

In 1915 Hasselbalch rewrote the Henderson equation to use Sorensen’s logarithmic pH. The result was the Henderson-Hasselbalch equation.

$$pH = pK' + \log[HCO_3^-/(S \cdot PCO_2)]$$

where S is the solubility of CO_2.

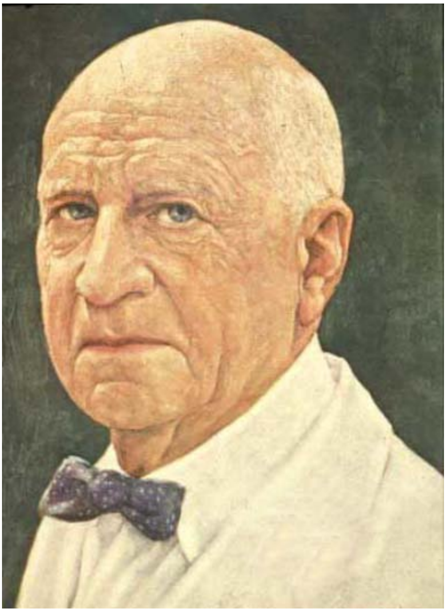
In order to measure the PCO_2 in blood, Hasselbalch solved the HH equation for PCO_2.

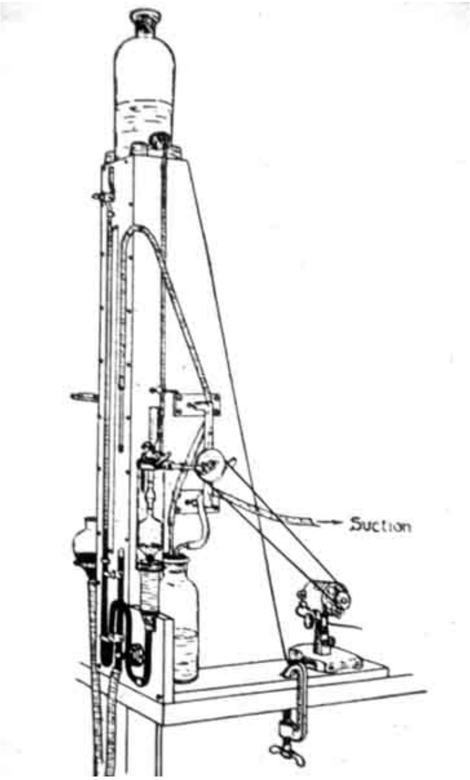
$$PCO_2 = CCO_2/(S(10^{(pH-pK')} + 1)$$

where CCO_2 is the total plasma CO_2 content, measured with the Van Slyke manometric analyzer after acidifying the sample to convert bicarbonate and carbonate to gas CO_2.

Donald Van Slyke invented this manometric analyzer to measure total plasma CO_2 content after acidifying the sample to free carbonate and other forms. I used it for about 10 years.

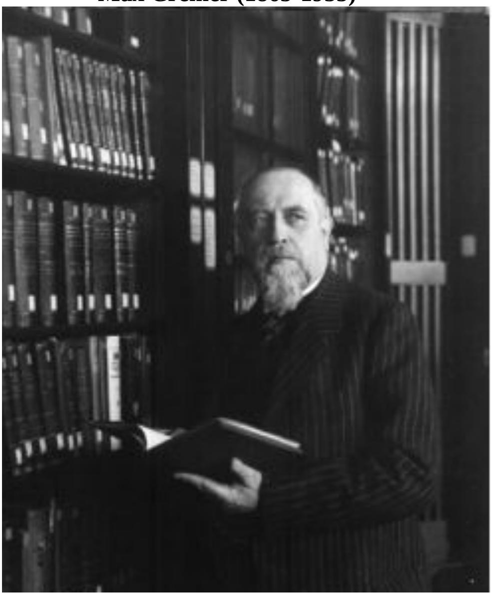
Donald van Slyke (1883-1971)





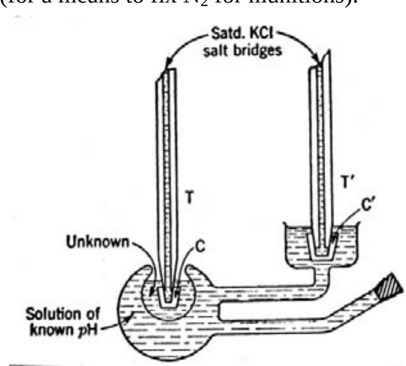
THE INVENTION OF A GLASS pH ELECTRODE

Max Cremer (1865-1935)

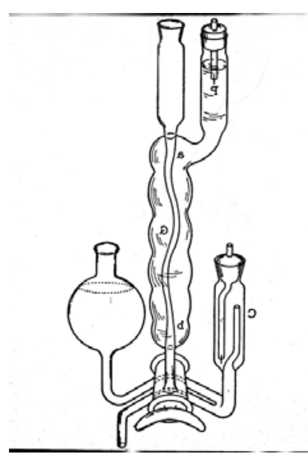


Fritz Haber (1868-1934)

Max Cremer in Germany discovered in 1905 that a thin poorly annealed glass membrane actually leaked hydrogen ions, generating a trans-glass electrical potential. He wrote in 1905: ***"The idea that glass as a diaphragm between the two liquids may possibly lead to a rather considerable electromotive force obviously did not occur to anyone."*** In Berlin in 1909 physical chemist Fritz Haber used Cremer's report to invent the first pH electrode using poorly annealed thin glass. When such glass separated two solutions of different H+ ion concentration, the potential difference was precisely proportional to pH difference. Haber was awarded a Nobel Prize in 1918 (for a means to fix N_2 for munitions).



In 1925 to keep CO_2 in blood samples Phyllis Courage made a cup pH electrode with a small opening. MacInnes and Belcher, with Corning, in 1930 made the first accurate blood pH electrode by putting blood inside a capillary of pH glass. The capillary, sealed at both ends to the external glass, needed curves to prevent breaking by temperature change.



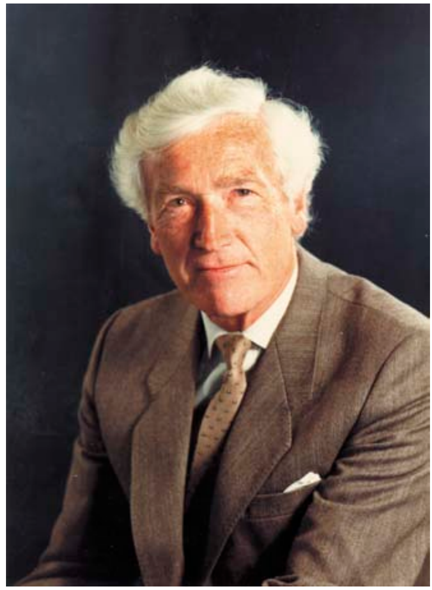
THE WORLD WIDE BULBAR POLIO EPIDEMIC

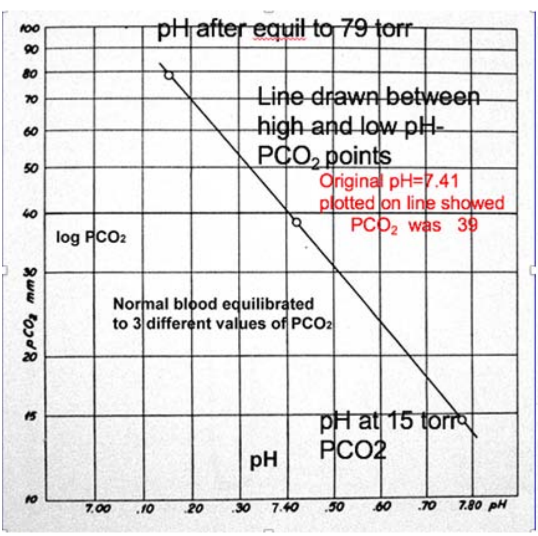
When the polio epidemic hit in 1950, artificial ventilation was needed for thousands of mostly very young kids. Doctors had to decide how much to ventilate by measuring arterial PCO_2. But labs couldn't manage the flood of samples. This photo was taken in Copenhagen's communicable disease hospital that became the world's first ICU. Director Dr. HCA Lassen asked an anesthetist Bjorn Ibsen, for help. They only had one ventilator, a Swedish Engstrom. Ibsen showed others how to use a bag and mask method to manually ventilate the patients through a tracheotomy tube. At one time when the epidemic peaked in late 1952, there were as many as 70 paralyzed patients manually ventilated by volunteers, student and nurses, taking 6 hour shifts. Ibsen became the world's first ICU director. He asked the Clinical Chemist Poul Astrup to measure $PaCO_2$ of the ventilated patients to help the volunteer untrained student bag-squeezers know how much they needed to ventilate patients.

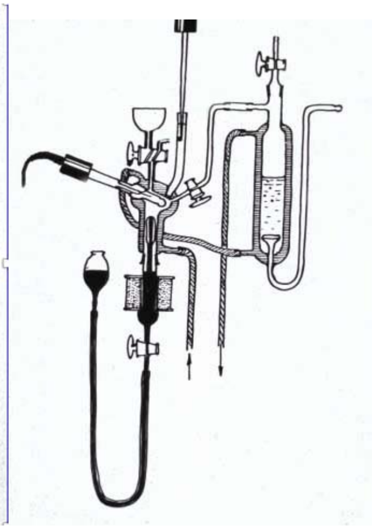
At first, Astrup had to use the Henderson Hasselbalch equation, placing his only pH electrode in his 37^oC culture room. Astrup found a 1930 diagram by Van Slyke showing that the relationship of log PCO_2 to pH is linear. He measured pH of arterial blood from the patient, and then remeasured the pH after equilibration of the blood at known high and low PCO_2 levels. He then drew a straight line between the known gas points. The patient's PCO_2 is found where a straight line meets the patient's pH.

Bjorn Ibsen (1915-2007)

Paul Astrup (1915-2000)

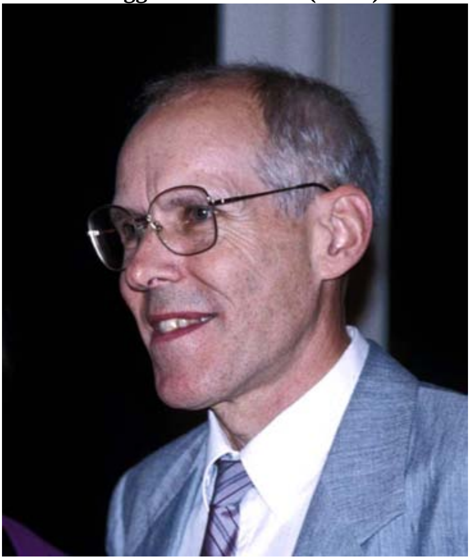




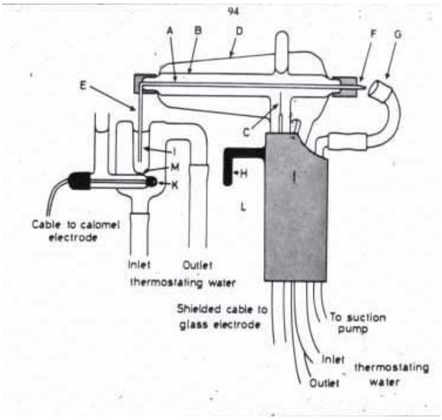


In 1953 Radiometer built Astrup this pH electrode in a 37°C water jacket for equilibrating blood with known gases.

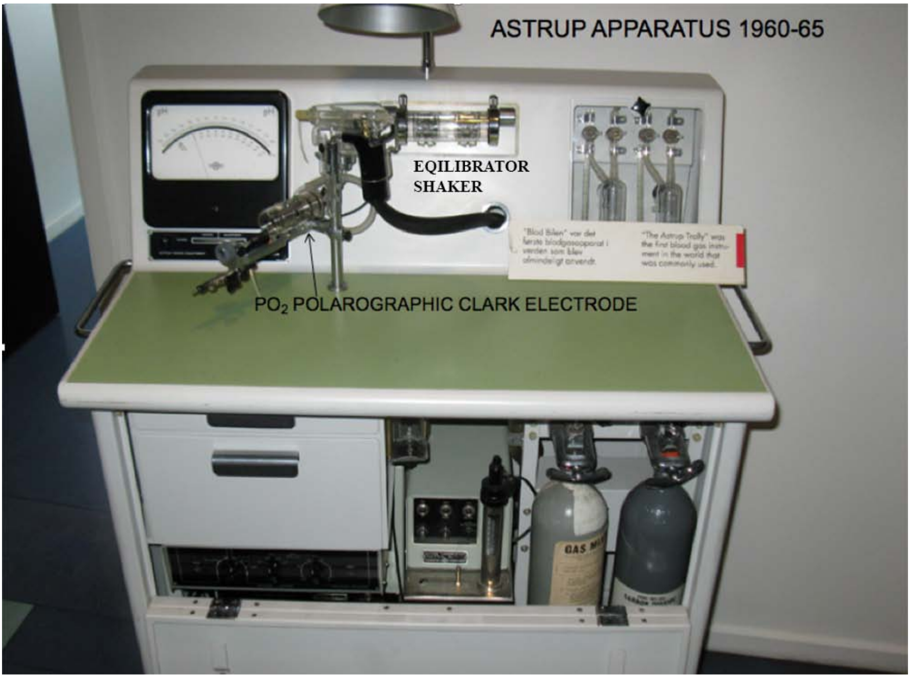
Ole Siggaard-Andersen (1932-)



Astrup's associate Ole Siggaard Andersen devised a capillary pH micro-method, filled by suction. He later introduced the concept of Standard Base Excess, SBE.

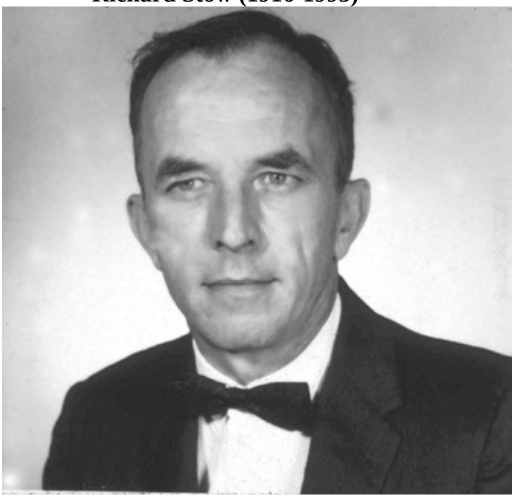


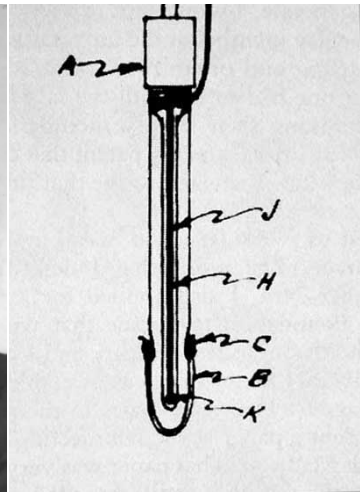
This Astrup and Siggaard-Andersen designed Radiometer apparatus was used to measure PCO_2 by Astrup's equilibration method. This apparatus was sold to hospitals worldwide for polio patients being artificially ventilated.



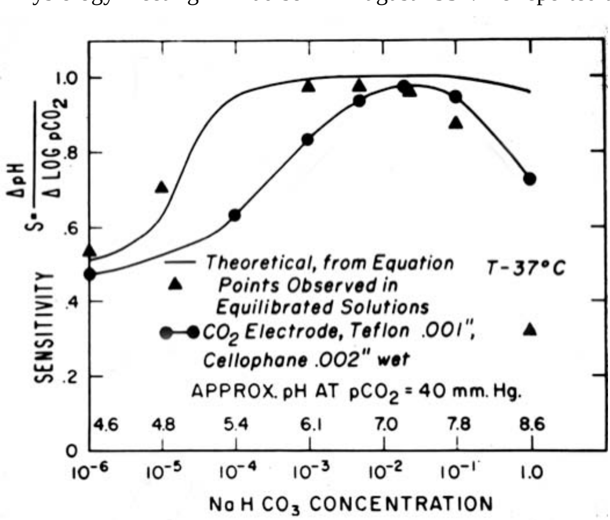
RICHARD STOW'S INVENTION: A PCO_2 ELECTRODE

Richard Stow (1916-1995)



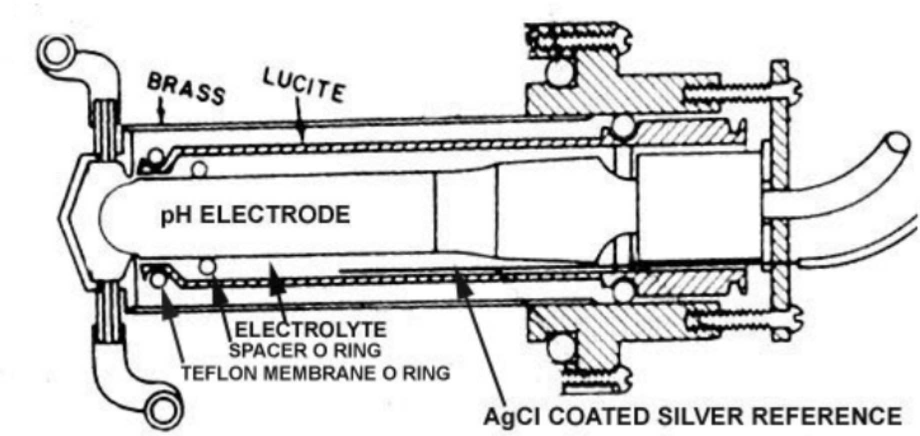


In 1953-4, Richard Stow was in charge of artificial ventilation in a polio ward in Columbus, Ohio. After using the old HH method, he conceived a way to make a blood PCO_2 electrode. As an expert glass blower, he built a combined pH and reference electrode. He wrapped a latex glove over the pH sensor wet with distilled water. Its potential responded to CO_2 but not to acid. He offered to sell the idea to Beckman but they declined. He presented this sketch at the fall Physiology meeting in Madison in August 1954. He reported that it drifted too much to calibrate.

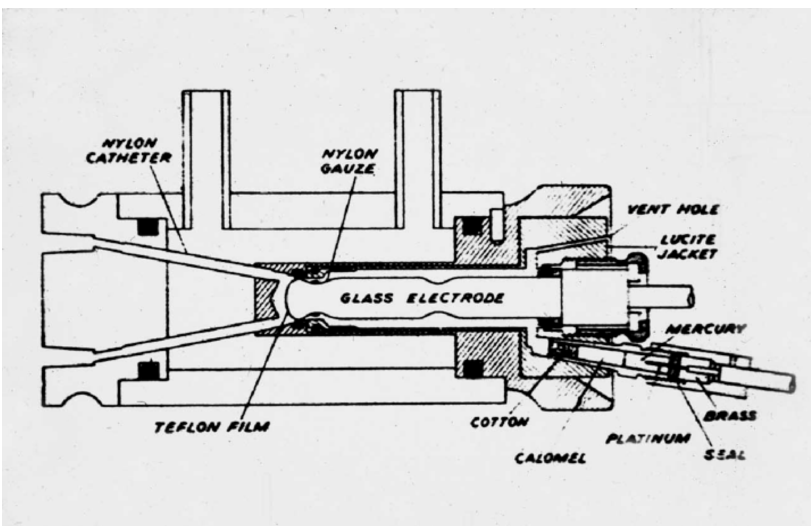


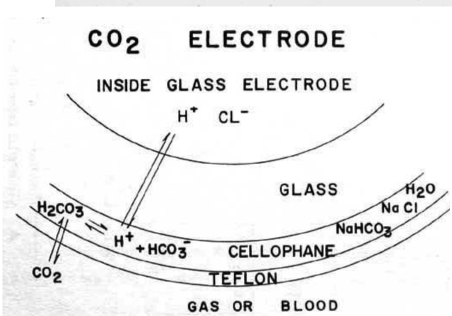
I asked him whether he considered adding bicarbonate to the water between latex and glass. He said bicarbonate was a buffer that would prevent any signal due to CO_2. He agreed for me to try it, assuming I would fail. A few days later I made a similar electrode. Adding a layer of cellophane wet with 25 mm sodium bicarbonate doubled the signal and stabilized it.

Stow refused to file a patent but deserves credit for the brilliant idea of a CO_2 electrode. This diagram shows the sensitivity ($pH/\log PCO_2$) as a function of the bicarbonate concentration. Without bicarbonate (left side) sensitivity is down to half. The best bicarbonate for speed and sensitivity is about 5 mM/l. The peak signal is 1 pH unit per decade of PCO_2 change.



My 1955 design of a CO_2 electrode used a thin cellophane spacer wet with bicarbonate electrolyte held over the pH glass by a 6 micron teflon membrane and O rings. It was immersed in a $37^{o}C$ thermostat with an oxygen electrode to make a blood gas analyzer.





The above design of a Stow-Severinghaus PCO_2 electrode for use with a circulating thermostat was built and sold for 3-4 years by National Welding.

Schema of a CO_2 electrode

THE BLOOD POLAROGRAPHIC OXYGEN ELECTRODE

Jaroslav Heyrovsky (1890-1967)

The Nobel Prize in Chemistry in 1959 was awarded to Jaroslav Heyrovsky "for his discovery and development of the polaro-graphic methods of analysis". He was born and lived from 1890 to 1967 in Prague. In the Institute of Analytical Chemistry of the Charles University, Prague, he was promoted to Associate Professor in 1922 and in 1926 he became the first Professor of Physical Chemistry.

He discovered that the current flowing into a 0.6v negatively charged platinum electrode in solution is directly proportional to PO_2, a method called polarography. Heyrovsky's invention of the polarographic method dates from 1922 and he concentrated his whole further scientific activity on the development of this new branch of electrochemistry. He was himself in the forefront of polarographic research for 40 years.

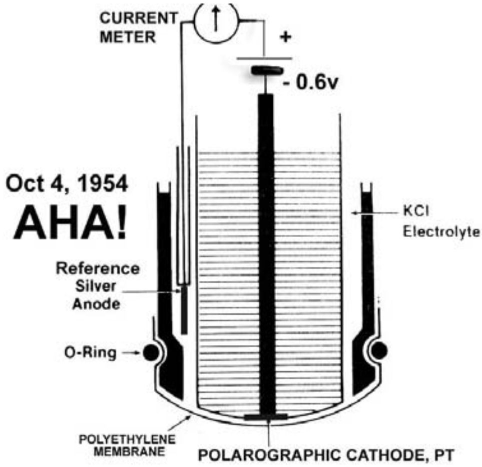
BIOCHEMIST INVENTS AN OXYGEN ELECTRODE

Leland Clark (1918-2005)

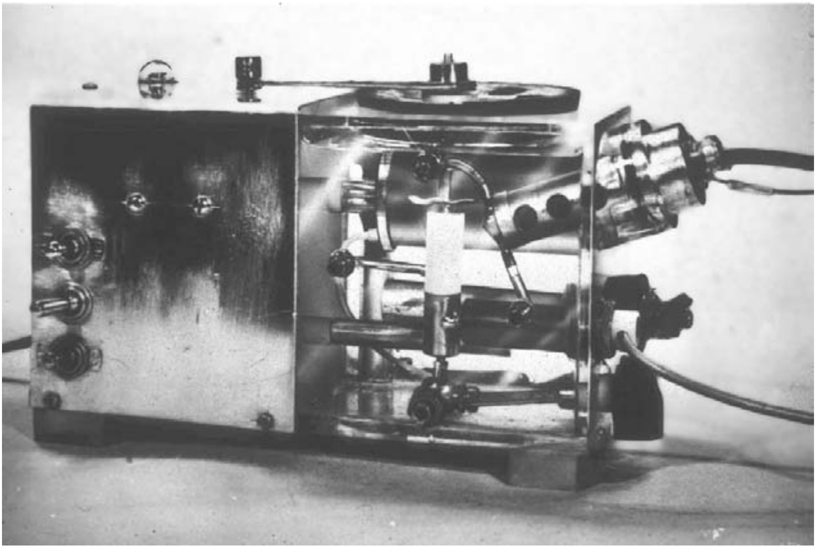
Clark was studying enzymes being generated in excised animal livers. He perfused organs with oxygenated blood from an oxygenator he invented shown here.

To measure its output oxygen saturation, in 1954 he invented a polarographic cathode oxygen electrode. To prevent blood from touching the cathode, he covered the cathode and its reference electrode with an oxygen permeable membrane such as polyethylene over a spacer to hold a saline electrolyte. To his surprise and delight, it worked. The local Yellow Springs Instrument Company built his design and he patented it.

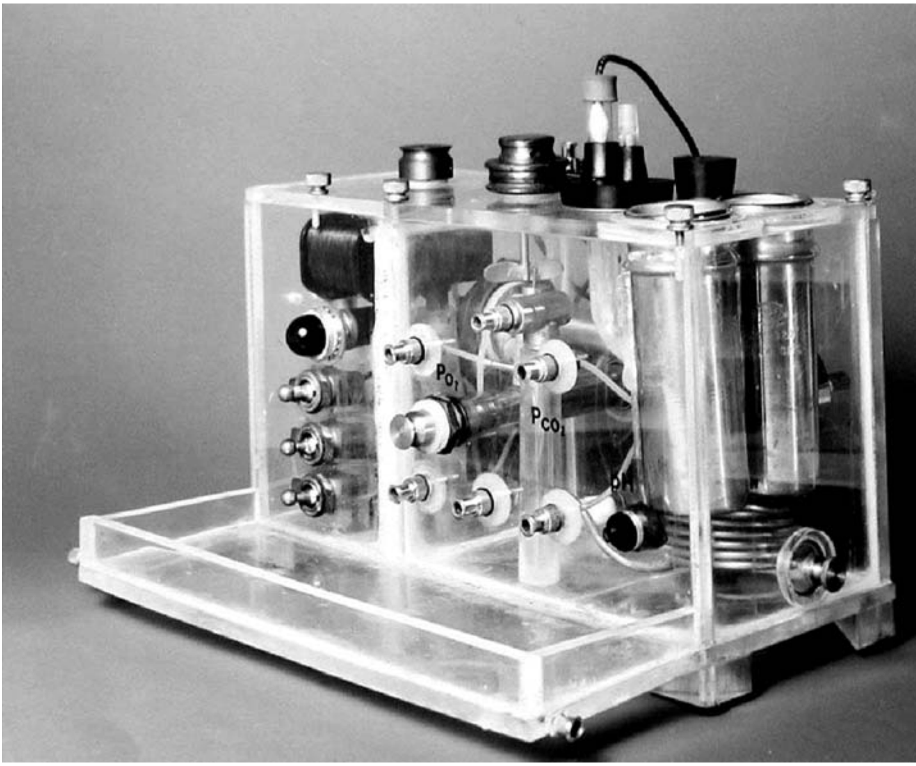
Beckman bought his patent in 1955 and rewrote it, making a claim for all electrodes using semi-permeable membranes to separate samples from electrodes.



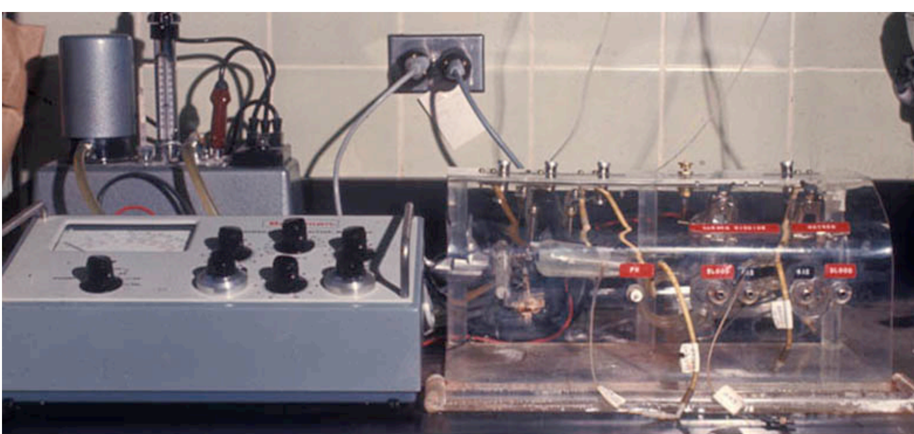
In April 1956, Clark revealed this patented oxygen electrode at FASEB. The 2mm diameter platinum cathode consumed oxygen from blood near its surface, severely reducing the measured PO_2 signal. The blood sample needed to be rapidly stirred. My technician Freemen Bradley and I designed this first ABG water bath containing both a Stow-Severinghaus PCO_2 electrode and a blood sample stirrer at Clark's PO_2 electrode. Before constructing it, I moved from NIH to Iowa City for a second year of anesthesia residency. This design was constructed by the physiology shop personnel in Iowa City.



I exhibited this first ABG at the fall 1957 ASA meeting and at the spring 1958 Experimental Biology (FASEB) meeting and published it in the J Appl Physiol in March 1958. At John Nunn's invite, I went to the first international blood gas analysis meeting in London in Dec. 1958.



In July 1958, I moved from NIH to UCSF. Beckman had reduced the Clark 2mm diameter to 10 microns eliminating the need for stirring. I added a MacInnes-Belcher pH electrode, making this the first 3-function blood gas analyzer. Copies were installed in the OR and ICU in the UCSF Moffitt hospital in 1959-60.

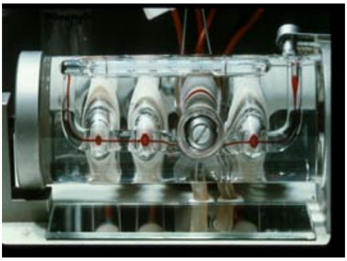


This ABG was installed in Moffitt ICU 1962 with Spinco blood gas analyzer readout.

We assembled this cart containing the analyzer and a commercial meter. It had a standard pH buffer and a tank of 5% CO_2 in air for calibration. Anesthesia techs, residents and faculty quickly learned how to use it.

The first commercial ABG, made in 1960 by the Yellow Springs Instrument Co, included PO_2 and PCO_2 electrodes and a tonometer to prepare blood from the patient for electrode calibration, but no pH electrode. Over the next decade many firms built replicas.

After many designs, about 1967 some of the analyzers became automated, self-calibrating, requiring less than 1 ml sample, with a printer. This example was built by Radiometer.



The 3 electrodes were soon miniaturized into 3 sequential glass cuvettes as in this Radiometer example about 1968.

Forrest Bird, the inventor and maker of a ventilator, visited the OR to persuade us to use his small ventilator with an anesthesia machine for intra-operative artificial ventilation. When he saw this blood gas analyzer cart with its lab-made CO_2 electrode, he offered to have it made by the firm in San Francisco building his ventilator, the Natl. Welding Co. I accepted. Bird and I became lifelong friends.

This small BIRD ventilator was widely used in intensive care and soon was also used in surgery for ventilation of paralyzed patients.

Forrest Bird was awarded the National Medal of Technology and Innovation by President Obama in 2009. Notice his unique invention fold-down glasses.

LAWSUIT

Ryan Neville, MD

Leland Clark PhD, 1978

In 1966, Beckman sued Dr. Ryan Neville in San Francisco for infringement of the Beckman revision of Clark's patent. Neville was marketing an aviation gas oxygen measurement cell containing a polarographic oxygen electrode. Neville’s lawyers somehow obtained and revealed in court a copy of the letter Stow wrote to Beckman in 1954 before they rewrote Clark's patent to include any semipermeable membrane. Beckman's lawyers knew they were in trouble. They had deliberately ignored Stow’s letter in their revised Clark patent.

In 1970, a federal appeals court finally ruled that Beckman’s patent was fraudulent. Beckman paid Neville triple damages 16 years after Clark’s invention.

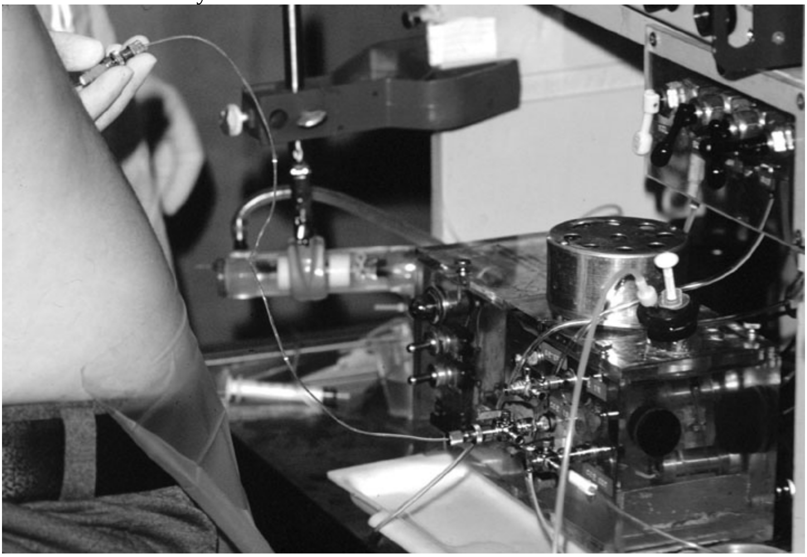
Clark told me that Beckman never paid him fully for his valid patent.

Clark’s electrode was the key discovery that launched the billion-dollar blood gas analyzer business. Fifty years later every blood gas analyzer contains a Clark type polarographic electrode.

THE USE OF BLOOD GAS ANALYZERS AT ALTITUDE

In 1962 we took a 3-function ABG to the UCSF high altitude Barcroft lab at 12,470 ft. altitude on California's White Mt range east of the high Sierras seen in the background. We studied blood and spinal fluid in each other during acclimatization.

At Barcroft in this shot we connected the spinal needle directly through nylon catheter to the ABG to avoid loss of CO_2. This home-made ABG was also used for altitude native studies in Peru and Bolivia in the early to mid 1960s.



One BGA made by Siemens, compact enough, was used for analyzing blood samples drawn from four Everest climbers at 8400 M and measured after being rapidly run down to the waiting BGA in a tent at 6400 M altitude 10 years ago today.

In conclusion, I summarize what I contributed to ABG: I heated for pH, added soda for CO_2, stirred for O_2, demonstrated to colleagues, published without patents and donated for patients. I watched my gadgets grow for 60 years until a few crazy, brave mountain-climbing anesthetists in my grandchildren's generation took an ABG up Everest so they could stick needles in each other's groins, something worth celebrating 10 years later even if half of the sticks may have sampled femoral veins, a rumor passed on to me by John West in March, 2017.

BGA 25th anniversary in 1983 with Stow, Astrup & Clark at FASEB

JWS