Electronics in the Development of Modern Medicine

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August 31, 2004

The practice of medicine relied upon bloodletting, incantations, and primitive chemistry until William Harvey discovered the circulation of blood in 1628. Once anatomy could be studied by dissection, the field of modern medicine, one of scientific exploration and clinical diagnosis, began in earnest.

A vast array of investigative, diagnostic, laboratory and therapeutic devices (including those which are implanted permanently in the body) now make use of the electronic technology that flowed from the invention of the Fleming valve.

Electrophysiology is the branch of physiology that is concerned with electric phenomena in living organisms. The evolutionary development of physiological instrumentation from electromechanical to electronic will be explored.

Before the valve, before De Forest's triode in 1907, the measurement of vital functions, such as the heart rate and blood pressure, were limited to human observation enhanced by the development of mechanical instruments, which could not measure electric potentials (as they were not yet known to exist). When vital currents were detected (nerves, muscles, the heart and brain), then electromagnetic instruments were developed to measure them.

The Galvanometer

In 1820, the Danish physicist Hans Christian Oersted reported that an electrical current passing through a wire deflected a nearby compass needle. The German scientist Johann Schweigger constructed his "multiplier," or multi-turn coil, which greatly increased the magnetic power of an electrical circuit and became the first accurate electrical measuring device, the galvanometer, which remains the basis for modern voltmeters and ammeters.

In 1825, Italian physiologist Leopoldo Nobili developed the astatic galvanometer, which removed the perturbation produced by the earth's magnetic field. In 1827, Nobili was the first to report measuring the current in a frog using any kind of an instrument.

Italian physicist Carlo Matteucci in Pisa followed Luigi Galvani's hypothesis of animal electricity. Using a very sensitive Nobeli's galvanometer, Matteucci was able to prove beyond a doubt that injured tissues generated an electrical current and that in fact, serial stacking of such tissue could multiply the current in the same fashion as adding more bimetallic elements to a Voltaic pile. Matteucci's work came to the attention of Johannes Müller, then the foremost physiologist in the world and professor at the medical school in Berlin.

Müller had been of the opinion that while electricity could stimulate a nerve, it was not involved in its normal function in any manner, that there was a mysterious "vital force." When he obtained a copy of Matteucci's book, and he gave it to one of his best students, Du Bois-Reymond. Within a year, Du Bois-Reymond had not only duplicated Matteucci's experiments, but had extended them in a most important fashion.

Du Bois-Reymond discovered that when a nerve was stimulated, an electrically measurable impulse was produced at the site of stimulation and then traveled at high speed down the nerve producing the muscular contraction. He had discovered the nerve impulse, the basic mechanism of information transfer in the nervous system.

Still, even if the existence of animal electricity had been established beyond doubt, many physiologists felt ill at ease with the galvanometer. When it came to analyzing the faint currents in muscles and nerves, they preferred an instrument that dispensed with electrodes entirely. For this they turned to what they called “the rheoscopic frog”, a detector invented by Galvani and later modified by Matteucci. Despite its grandiose name, the rheoscopic frog could not have been simpler – it consisted of a frog’s leg with the skin removed and a length of nerve left attached. The preparation was uncomplicated, convenient and inexpensive and, as long as it was not left sitting around for too long, quite reliable. The slightest charges touched by the nerve caused the leg to twitch unmistakably, no matter how transient or how faint the currents may have been.

Considering the rheoscopic frog’s advantages as a detector of animal electricity, one wonders why Du Bois-Reymond bothered with a galvanometer at all. Foremost was the galvanometer’s philosophical significance. Du Bois-Reymond felt he needed a physical device to demonstrate the identity of electricity in the organic and inorganic worlds. This principle of identity opened itself to challenge. If animal preparations were used to display animal phenomena – in the end, one could always argue that the phenomena were specific to animals.

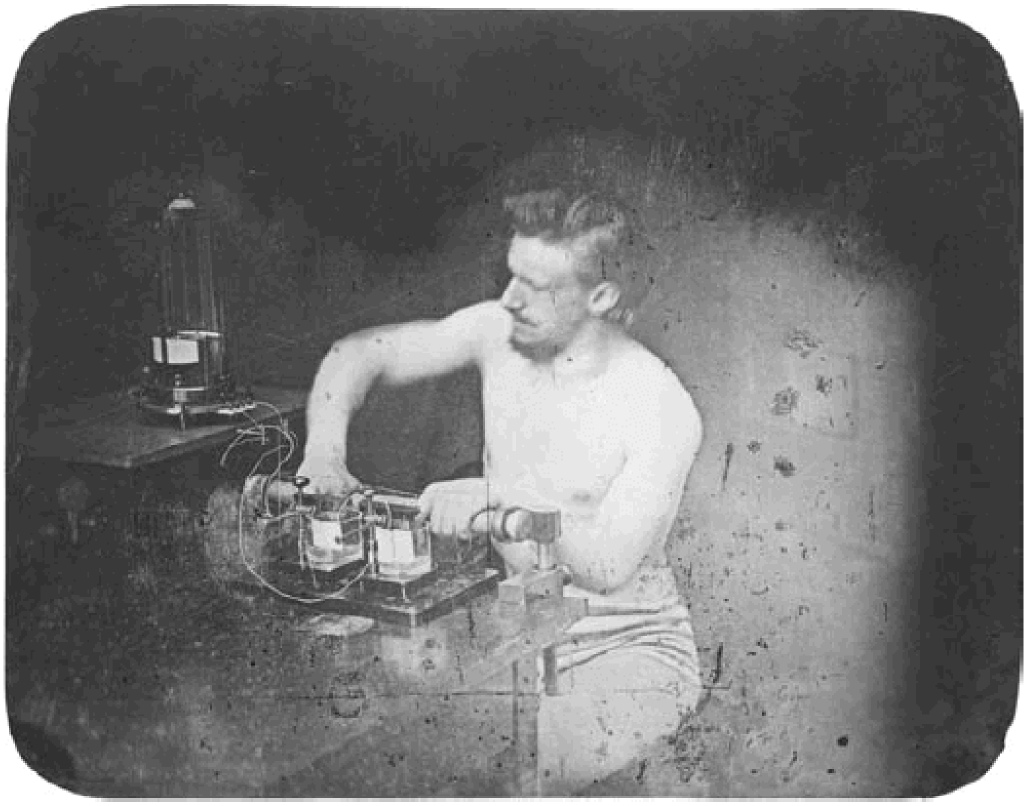

Figure 9. Photograph of Paul du Bois-Reymond, Emil's younger brother, demonstrating tetanic currents in his own body. The galvanometer used to detect the signal rests on a separate table by his right arm, the one he appears to be tensing. Note how the experimenter dips only his index fingers into the conducting vessels. The idea for the steadying wooden bar may have come from Emil du Bois-Reymond's experience with gymnastic equipment.

Figure 1 -Du Bois-Reymond

The capillary electrometer

The search for improved measuring devices continued until Gabriel Lippmann invented the mercury capillary electrometer in 1875. This electrometer is an exceedingly delicate electrical manometer.

Figure 2 - Capillary Electrometer

A rise of electrical pressure on the mercury side or a fall of electrical pressure on the sulphuric acid side, causes the mercury to move towards the point of the capillary; a fall of electrical pressure on the mercury side or a rise on the sulphuric acid side, causes the mercury to recede from the point of the capillary. The instrument accordingly is an indicator of "potential" or "pressure"; not of "current." Its delicacy is such that it will react to as little as 25 microvolts. It offers the following advantages: the indications are practically instantaneous, free of lost time, and of after-oscillation; the resistance in the circuit is immaterial; unpolarisable electrodes may for most purposes be dispensed with.

Augustus Waller was the first to discover that the electrical activity of the human heart could be recorded by Lippmann’s capillary electrometer without opening the chest to expose the heart. But Waller had a problem. He only got movement of a fraction of a millimeter for each heartbeat. He decided to project an image of the mercury, which would enlarge it. He then needed to record the pulses, and for this he had a really ingenious system. Waller shielded off all the light apart from that shining through the capillary column. He then put a photographic plate on a toy wagon, which was pulled along by a weight. Now, as the mercury went up and down, it interrupted the light casting a shadow and leaving the photographic plate unexposed behind the mercury.

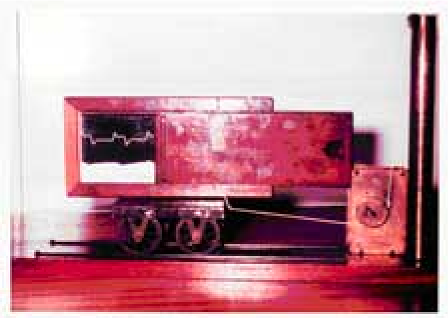

Figure 3 - Waller's film recording system

Then Waller had an idea. The body itself conducts electricity to some extent. So why not use the body itself instead of attaching electrodes to the heart? He envisaged using the limbs as sort of extension cables.   Waller set to work - on himself**.** To make electrical contact, he used metal bowls of salty water, into which he could dip hands or feet. What Waller discovered was that if he put his left foot in one basin and right hand in the other, he got an electrical blip on the trace. He carefully analyzed the traces and proved that a tiny fraction of a second before each beat of the heart there is an electrical blip. He had invented the electrocardiogram (ECG) and was the first person to record the electrical pulse of a working human heart in 1887. In his initial paper, he called the record an "electrogram". One year later, he called them "cardiograms". He often used his famous English bulldog "Jimmy" as his subject. Jimmy apparently enjoyed the work.

Figure 4 - Augustus Waller and his dog Jimmy

The String Galvanometer, the ECG and EEG

Wilhem Einthoven in Holland introduced the term we now use - the "electrocardiogram". He began to develop his own galvanometer in 1900, after being dissatisfied with the capillary electrometer.   His invention was known as the "string galvanometer" and was introduced in 1903, although Einthoven published a preliminary report on it in 1901. A quartz filament thread, coated with metal, lays between two poles of a magnet and is connected by wires with basins, which serve as electrodes. Filled with salt water, the hands and a leg of a patient are immersed in the basins. The electric current in millivolts produced by the movement of the heart chambers is conveyed to the thread causing it to move slightly. By means of light projection (light galvanometry) the movement is magnified and projected by microscope optics to be recorded on photographic paper on a rotating drum.

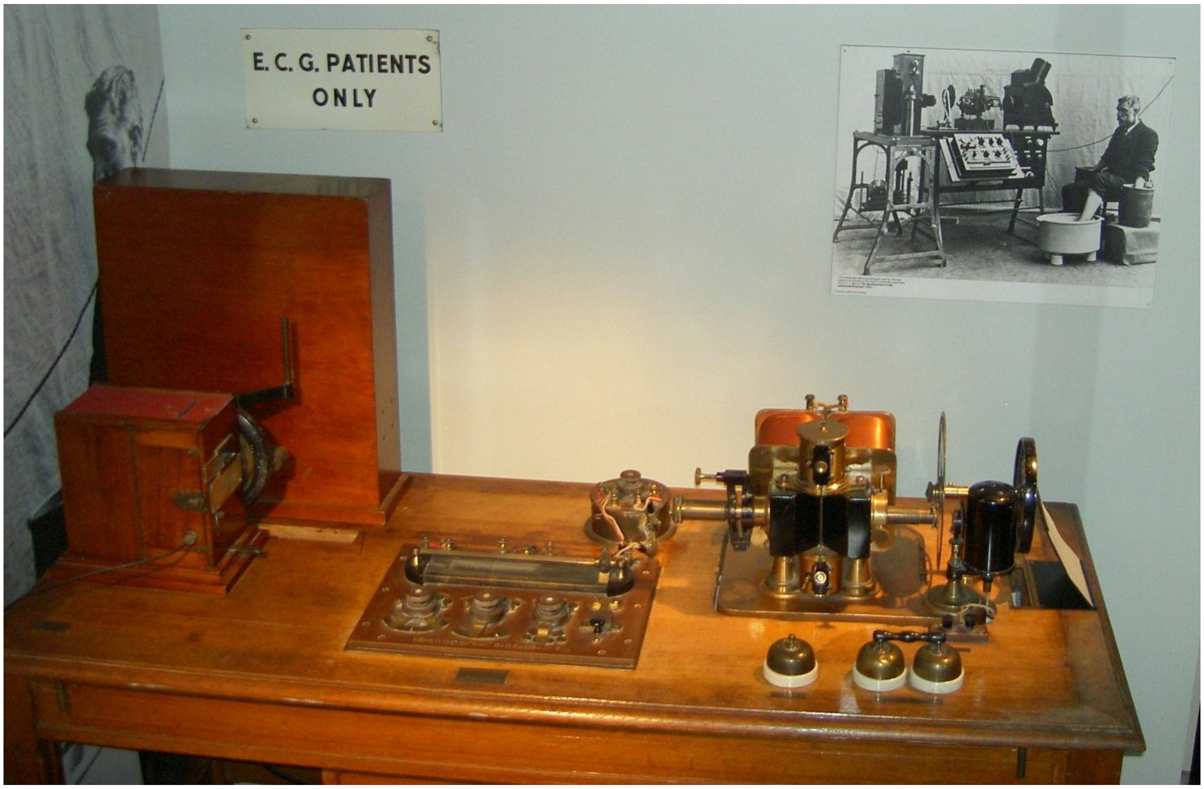

Figure 5 - Einthoven string galvanometer, London Science Museum

The string galvanometer led countless investigators to study the functions and diseases of the heart muscle. The laboratory at Leiden became a place of pilgrimage, visited by scientists from all over the world. For a very long time, long after Fleming invented the valve and De Forest the triode, the string galvanometer was the standard of reference in electrocardiography as Einthoven always mistrusted the use of electronics, fearing the distortion of curves. Edelmann and Sons of Munich initially manufactured Einthoven's electrocardiograph in Germany. He later went with the Cambridge Scientific Instrument Company, Ltd., of London for manufacture and this "CSI" instrument became "the" world standard in electrophysiology, in use by everyone.

It was the first instrument to have clinical significance and in 1924, Einthoven was awarded the Nobel Prize in Physiology or Medicine "...for his discovery of the mechanism of the Electrocardiogram."

The first string galvanometer EKG machine was introduced to the United States by Dr. Alfred Cohn - the Edelmann String Electrocardiograph. During the development of the string galvanometer, its size also was decreased from 600 pounds in 1903 to just 30 pounds in 1928. Professor Horatio Williams at Columbia University designed the first EKG machine manufactured in the United States. Charles Hindle constructed it in 1914.

Meanwhile, at Cambridge, Professor Edgar Douglas Adrian began investigating the sense organs by electrical methods. Adrian's first research work was done with Professor Keith Lucas, who was working on the impulses transmitted by motor nerves. Lucas was, at the time of the First World War, thinking of improving the study of the electrical currents in nerves by amplifying them by means of valves, a method which Adrian was later to employ. Cambridge Scientific Instruments Ltd. made and marketed several of Lucas's physiological instruments.

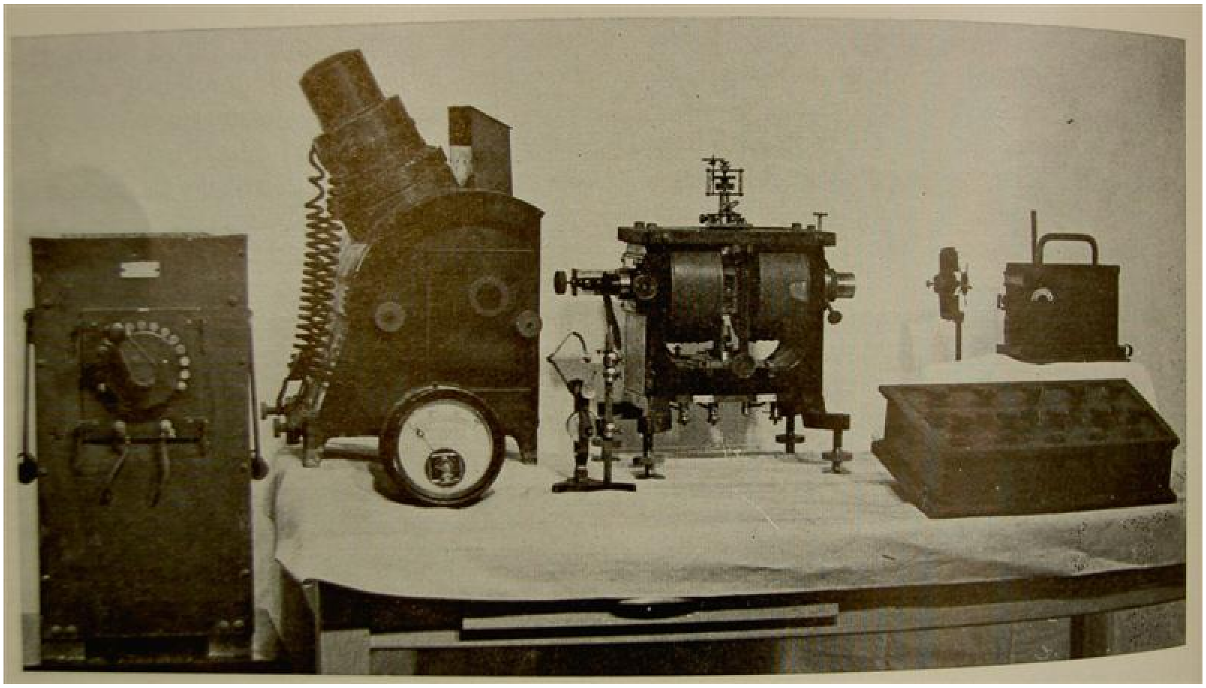

Figure 6 - Einthoven Edelmann electrocardiograph

Lucas's experiments were placed in the basement in Cambridge at the greatest possible distance from the rooms containing running machinery as the capillary electrometer was affected by vibration. Tragically, Lucas was killed in an airplane flight while doing experimental work for the R.A.E. Adrian inherited his laboratory and continued Lucas's work.

The electroencephalogram (brain wave recorder) or EEG was developed by Hans Berger at the University of Jena, Austria. Using metal strips and a sensitive galvanometer on a continuous roll of paper, Berger noted from 1924 to 1938, the patterns that laid the foundation for modern EEG studies. However, not until Adrian and Mathews (1934) published their classic paper verifying Berger's findings, was the reality of human brain waves accepted. In 1934, a small grant was awarded to Dr. Frederic Gibbs for instrumentation to process electroencephalographic data. His goal was to apply the knowledge gained by Hans Berger and confirmed by Adrian to clinical applications.

The Thermionic Valve

Physiologists were still faced with the major problem of measuring and analyzing the very small electrical signals that they were able to record. They were not alone; adequate amplification was an acute problem in the then young telegraphic industry. Several scientists facilitated the introduction of valve amplification into physiology, especially Professor Alexander Forbes from Harvard, Herbert Gasser in St. Louis, and Adrian and later his undergraduate student, Bryan Mathews in Cambridge.

Adrian and Forbes had met before World War I, when Forbes spent a year (1911-12) working with Sherrington in Liverpool. Forbes also visited Lucas. Forbes was so stimulated that when he returned to America, he had "new ideas, new technologies and new equipment."

Forbes had served as a naval radio officer in World War I. Professor Williams had suggested to Forbes the use of the "electron tube" to amplify currents. It was "nothing new", according to Forbes, considering that radio had been using it for years, but the difference was that the telephone receiver was the output device. Forbes intended to drive the string galvanometer with the valve as telephone receivers are placed in series with the plate of the valve. This would be impossible to do with the string galvanometer, as it could not take the DC plate current. What to do?

Forbes decided to use a plate resistor with the valve, in place of the telephone and then couple across the plate resistor in series with a large (15 microfarad) blocking capacitor the galvanometer so that the action currents they were interested in, (most of the effect being over in less than 0.01 second) would be undistorted. This one-tube amplifier was battery powered. The laboratory had to make their own "B" lead storage battery and charged it from the 110V Mains. For projection, an arc lamp (via a cylindrical lens) focused a beam of light on the galvanometer then deflected by the galvo to a horizontal line across the film. They then constructed the camera to work with standard perforated 35mm moving picture film, sprocket driven by a 12VDC motor intended for an automobile self-starter at 460 rpm. Using a disk-clutch system to vary the motor speed, any recording speed from 7cm/sec to 48 cm/sec could be achieved. The film was used in 200-foot rolls.

Forbes amplifier achieved a 50-fold increase in sensitivity. He went on to develop many improvements to the amplifier. In 1937, with Albert Grass, reported the use of the newer pentode tube as the first stage since their plate voltages may be varied over wide ranges without changing the plate current appreciably; the sensitivity was 1 or 2 uV peak and a drift of 10 uV per minute (half that if allowed a 2 hour warm-up). Batteries continued to power the amplifiers.

In early 1921, Adrian had invited Forbes to Cambridge and asked him to "bring over some valves". Forbes and Adrian constructed a single triode amplifier and Adrian chose to use it to drive a capillary electrometer instead of the string galvanometer. Apparently as even with the capacitor, the string could be broken by overdriving it. Also, Adrian had the microscopic analyzing system and its records could be analyzed within a few moments (instead of having to develop the motion picture film). The high resistance of the electrometer better matched the output of the amplifier and more importantly, it was more robust and foolproof. Adrian had many good results with the equipment and went on to build a three-valve amplifier (although two valves were usually all that were needed).

Shortly afterwards, Bryan Mathews developed a sensitive moving iron oscillograph which was better than either the galvo or electrometer amplified systems. While he realized that eventually, CRT oscilloscopes would be the best device to use, at the time, the light intensity was not high enough to write on film fast enough to capture the nerve potential signals.

In the Matthews system, the potential to be recorded (amplified by a valve amplifier) is applied across the coils of an electromagnet and the movement of an iron tongue registers the alteration produced in the field. Attached to the tongue is a small mirror and the resulting system had a natural resonance frequency of 5000 Hz, so it was a very fast device. He could either use photographic plates or moving film from 10-50 cm/sec. He used a standard three-stage resistance coupled amplifier and followed it with another amplifying stage followed by two paralleled valves driving the coils. The response of the system was 200 microseconds for a 95% excursion of the beam. Mathews stated that the unit was electrically unbreakable and mechanically very robust. Adrian, in most of his work, used the moving iron oscillograph after 1928.

For his work about the functions of neurons, Adrian was awarded, jointly with Sir Charles Sherrington, the Nobel Prize for 1932.

The development, and increasing use of equipment, such as the valve amplifier, altered not only the experimental design and possibilities, but also changed the whole ambience of the electrophysiological laboratory, which had, previously looked and sounded more like a boiler room than a laboratory.

In 1935**,** Dr. Gibbs approached Albert Grass, a recent graduate of MIT, to design three devices to amplify human EEG potentials. Grass did so, defining the foundation of Grass Instrument Company, and of EEG technology. In 1936**,** while working at Harvard Medical School, Grass designed moving coil galvanometers, which enabled the embryonic EEG instrumentation to accurately and reliably record the EEG frequencies on chart paper. The addition of these new galvanometers to his early amplifiers became the Grass Model I, used by Gibbs, Lennox, Davis and others. Cannon, Rosenbluth and Renshaw used this same amplifier design in early neuromuscular studies. In 1938, the Grass Model II was developed and used by doctors to evaluate head injuries and the condition of airplane pilots as World War II begins in Europe.

The Oscilloscope

Michael Faraday turned his attention to passing electric currents through tubes evacuated of air. In such ‘vacuum tubes’, he noted the dark spaces, which formed in front of the cathode at very low pressures, and the phosphorescence of the glass, which, by 1876, was shown to be due to ‘cathode rays’.

In 1897, on February 15th, Ferdinand Braun at the University of Strasbourg in Berlin announced that he had invented and developed what he called his "cathode ray indicator tube." Coupled to photographic film to make a permanent record it would become the fastest electric recording instrument.

In Braun's original cathode ray tube (CRT), the oscillatory electrical current to be observed flowed through a coil wrapped around the discharge tube. This resulted in a vertical deflection of the electron beam proportional to the intensity of the oscillatory signal being measured. The trace on the face of Braun's CRT was merely a vertical line. The horizontal deflection of the image to create a "time" axis was achieved by means of a small rapidly rotating mirror placed in front of the CRT. Electrostatic horizontal deflection of the electron beam was achieved by one of Braun's assistants in 1910.

Characteristic of Braun's attitude toward scientific discovery, he never patented his cathode ray indicator tube. Rather, he published a detailed description of how his tube was constructed so that any scientist could build one. In 1909, the future importance of the CRT was not at all clear to the Nobel Prize Committee members. What was clear, however, was that wireless telegraphy already was profoundly changing the way the world communicated. It was for this reason that the Nobel Prize Committee recognized the separate, but equally important, complementary wireless telegraphy achievements of Braun and Marconi. While Marconi's accomplishments were more spectacular and much more highly publicized, Braun's achievements were no less important to the overall development of wireless telegraphy.

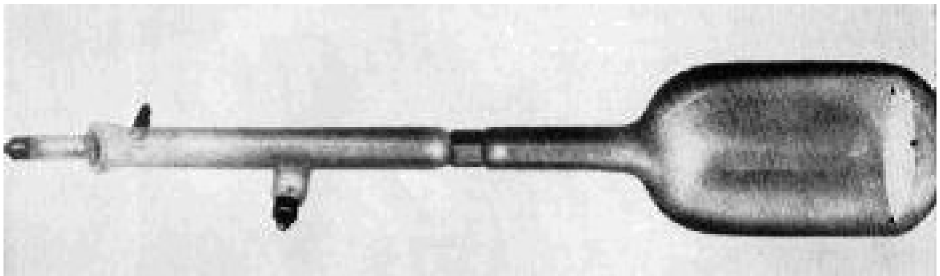

Figure 7 - Braun Cathode Ray Tube

The original Braun tube was a cold cathode tube. It did not contain a filament for electron emission and only about one-third of the electrons passing through a hole in the aluminum plate (between the anode and phosphor screen) striking the phosphor screen. It requires 10,000 to 20,000 volts between the cathode and anode to operate.

Early oscilloscopes were useful for the electric power industry but not for physiologists. The recording speed of early photographic films was so slow, that to make a recording, at least 15-20 sweeps of the beam would be required and they had to be identical. Another minor disadvantage was that the abscissa (time) axis depended on the discharge of a capacitor, which is logarithmic. The photographic records had to be redrawn, with corrections for this distortion. Gasser and Newcomber at Washington University in Pennsylvania in 1928 obtained approximately linear sweep by placing a vacuum tube in series with the timing capacitor.

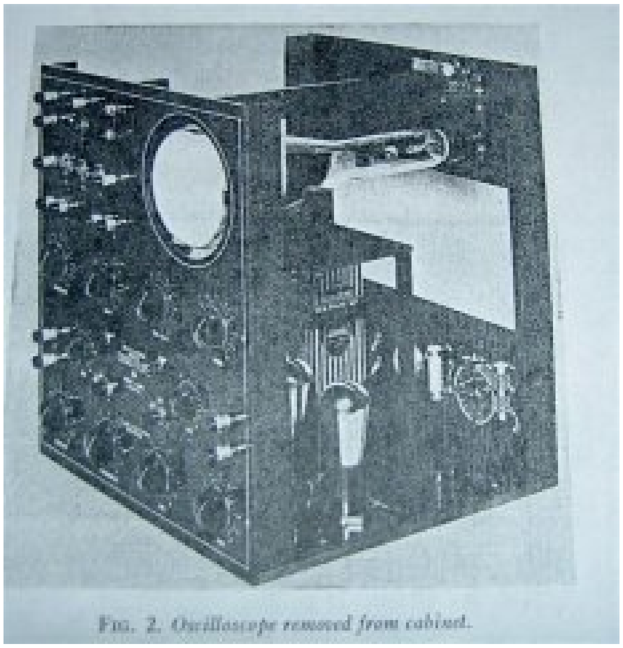

FIG. 2. *Oscilloscope removed from cabinet.*

Figure 8 - Bedell and Kuhn Oscilloscope, 1929

In 1937, Erlanger and Gasser introduced the oscilloscope as a biomedical device to investigate electrophysiological events. They showed that nerve fibers, according to their conduction velocities, could be divided into three main groups of which the first, group A, could be further subdivided. A large number of other properties of the nerve fibers vary with the speed of conduction. For instance, the duration of the impulse, its rate of rise, its size, the duration of the unexcitable, or refractory period following each impulse, the threshold of excitation, the sensitivity of the discharge to pressure on the nerve and to asphyxia, was an array of properties connected with impulse conduction, all of which need not vary in an exactly parallel manner.

In the brain and the spinal cord the time ratios of the impulses are of primary importance for the cooperation of the nerve cells. A difference of 0.001-0.005 seconds in the time of arrival of impulses means that a given path may be found opened or closed for their passage onwards. Problems of this kind belong to the present-day program of experimentation in these fields.

Allen B. Du Mont started his career in electronics with the Westinghouse Lamp Company when the company was making 500 radio tubes a day. He left the company four years later to join the De Forest Radio Company as chief engineer. At De Forest Radio, Dr. Du Mont first began working with television, using the whirling disk technique. Unable to interest his superiors at De Forest in the cathode ray tube as a better approach to television, Dr. Du Mont, resigned to start his own laboratory. In 1931 he founded Allen B. Du Mont Laboratories, Inc., in his garage laboratory at his home, with $1000 (half of it borrowed).

The company achieved its initial success as the primary U.S. manufacturer of cathode-ray tubes, which had become critical to the electronics industry. Dr. Du Mont developed a cathode ray tube that could be manufactured relatively inexpensively and lasted for a thousand hours. Until Dr. Du Mont's discoveries, cathode ray tubes were imported from Germany at high cost. They burned out after 25 or 30 hours. The tubes developed by Du Mont were much better; they lasted for a thousand hours.

Figure 9- Early Du Mont 5” cathode ray tube circa late 1930's

There was virtually no market in television at that time for his improved tubes; the gross income from sales the first year was only $70. However, a successful by-product of his television work was the cathode ray oscillograph. While Dr. Du Mont kept at work on television, the laboratory, which was incorporated in 1935 as Allen B. Du Mont Laboratories, Inc., prospered through the sale of oscilloscopes but they were still not very useful for physiological measurements. They did not have a triggered time base.

World War II

By WW II, a variety of investigators had begun using electronic equipment to study the genesis of bioelectric potentials, the action potential, the electroencephalogram, the electromyogram, blood flow, and blood pressure.

The war had a profound affect on the advancement of electronic instrumentation as a great deal of money was spent on the development of instruments for wartime needs. After the war, medical and physiologic laboratories began to accumulate and use this equipment. Due to limited funding, low-cost war surplus electronics provided many components (amplifiers, recorders, and instruments).

Even in the late 1940’s and early 1950’s, it was unusual to find a physician or even a biologist or physiologist who could design more than an elementary electronic instrument. Only since 1945, was the use of electronics use in medicine greatly expanded. Local parts suppliers were few, mostly for amateur radio enthusiasts and the repair of commercial radios (which at that time were the most common form of manufactured electronics.”)

Well before the end of World War II, Howard Vollum had conceived the idea of a new kind of oscilloscope. His work with radar, during the war in the U.S. Army, had shown that the commercially available scopes were simply too elementary and too limited to be of value in the future. Pre-war scopes could measure only repetitive or continuous events. As work went forward on radar and atomic research during the war, the military developed an oscilloscope with a triggered sweep circuit, enabling the user to see much faster events, although still only those events that were recurring. As was mentioned before, earlier scopes, such as the Du Mont, had an on-going sweep circuit. It started, ran to termination, when the signal being measured terminated, and then started over again. The military scope, called the Navy Synchroscope, had a triggered sweep circuit. It had a repetition generator built in, which would trigger the signal the user wanted to see, and simultaneously trigger the scope. The user could look at much shorter pulses, at his convenience, as he could trigger the event.

Dumont, RCA and Varian oscilloscopes were not very sensitive and could not pick up high-speed events. Vollum and his colleagues had solved the problem of high-speed pulses and transient events in their work in England, for they had developed simple (but highly effective) delay lines. Delay lines allowed the scope to trigger before the event was displayed on the screen. Scopes, during the war, were mostly qualitative. The scope Howard Vollum was about to manufacture with Jack Murdock in Portland, Oregon (at a company they called Tektronix) in 1947 was going to be different. The initial model was christened the “501”. The “5” stood for the 5-inch CRT and the “01” stood for Model 1.

By early 1947, the 501 had become the 511 with nine calibrated vertical ranges from 0.25 volt/cm through 200 volt/cm. The time base, or horizontal display, was calibrated in five ranges, from 0.01 second/cm to 0.1 microsecond/cm. The company was on it’s way to becoming a world leader in oscilloscope technology and it’s instruments would soon be found in most medical laboratories. New phosphors were developed that had short persistence making them ideal for film recording and dual phosphors were most useful for slow waveforms such as the EKG.

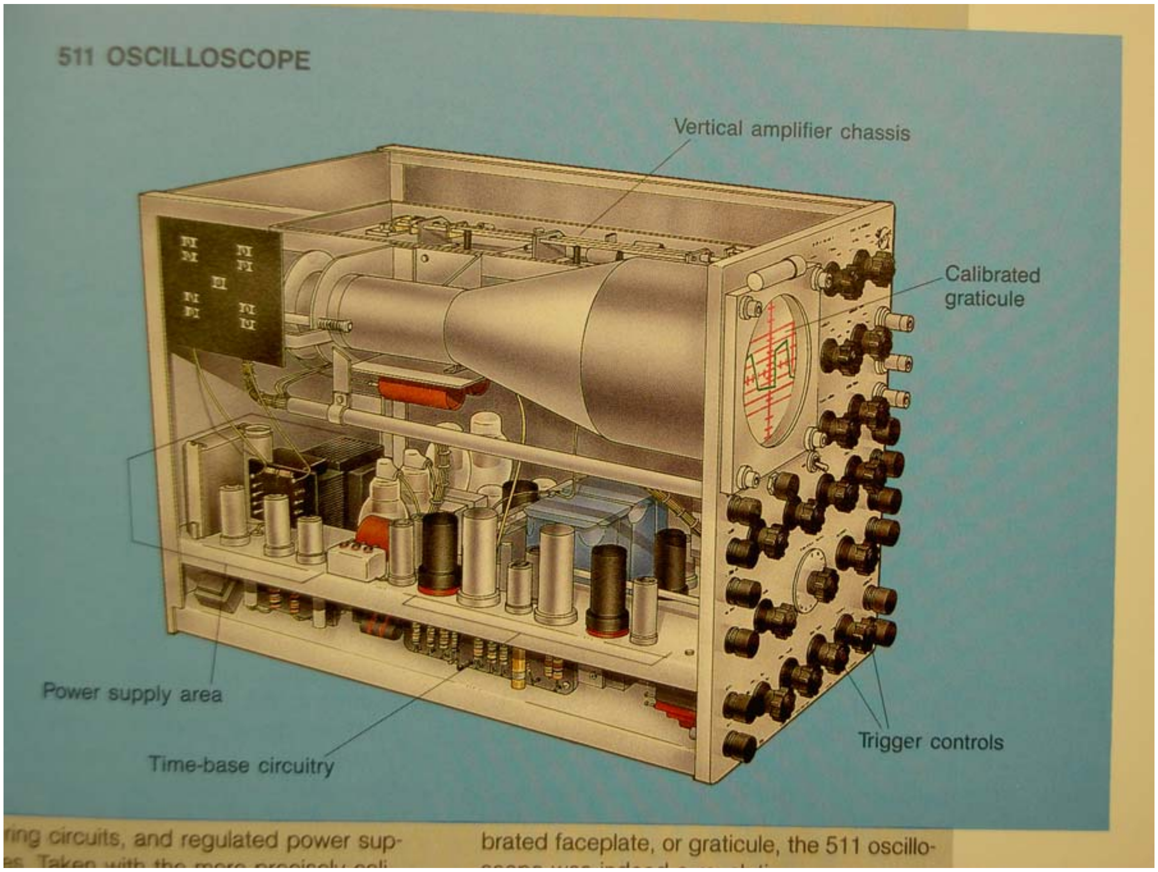

Figure 10 - Tektronix Model 511 Oscilloscope

The company offered medical research laboratories some factory modifications for the oscilloscopes. Later, they offered scopes with a variety of plug-in vertical amplifiers for all kinds of applications. For those who were entrepreneurial, Tektronix offered blank plug-in kits so they could build their own vertical amplifiers.

One such entrepreneur in San Francisco CA, was Seymour (Gus) Winston, the author’s mentor in electrophysiology instrumentation. He began his career at the University of California Medical Center in San Francisco in the Physiology Dept, as many did, after service as a radioman in the US Army in World War II.

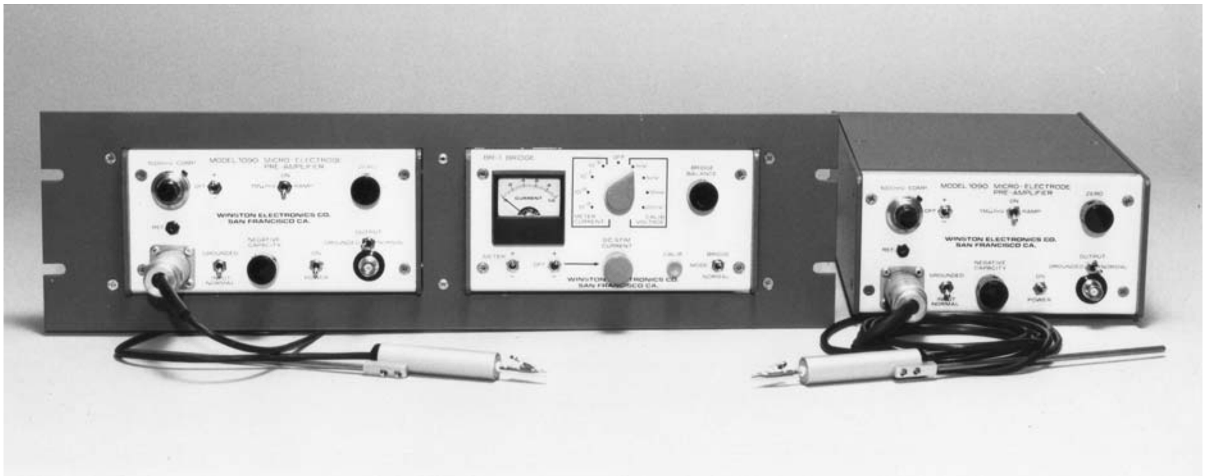

Figure 11 - Winston Electronics microelectrode preamp-bridge

For over 30 years, Winston developed electronic instrumentation for physiology research and clinical medicine. He was typical of the people developing such instrumentation, as the commercial market for medical research instrumentation was small.

In 1951, Winston built and sold under the Sutter Instruments name, the first commercial open chest AC cardiac defibrillator. Some products were electromechanical, like the Sutter Instruments microelectrode puller, which made microscopically small glass needle electrodes to puncture nerve cells to record intracellular potentials. In his home garage, in the evenings and weekends, Winston, the author and others (who also worked during the day at the university), would reproduce devices developed in the UCSF physiology department as well as develop instruments other university scientists desired. Winston Electronics modified Tektronix oscilloscopes by designing a microvolt input differential vacuum tube preamplifier plug-ins selling them as clinical EKG and EMG (electromyography) instruments (the EMGs used Grass stimulators). This was done before it was common practice to use CRTs as medical monitors; more common was the curvilinear strip chart recorder.

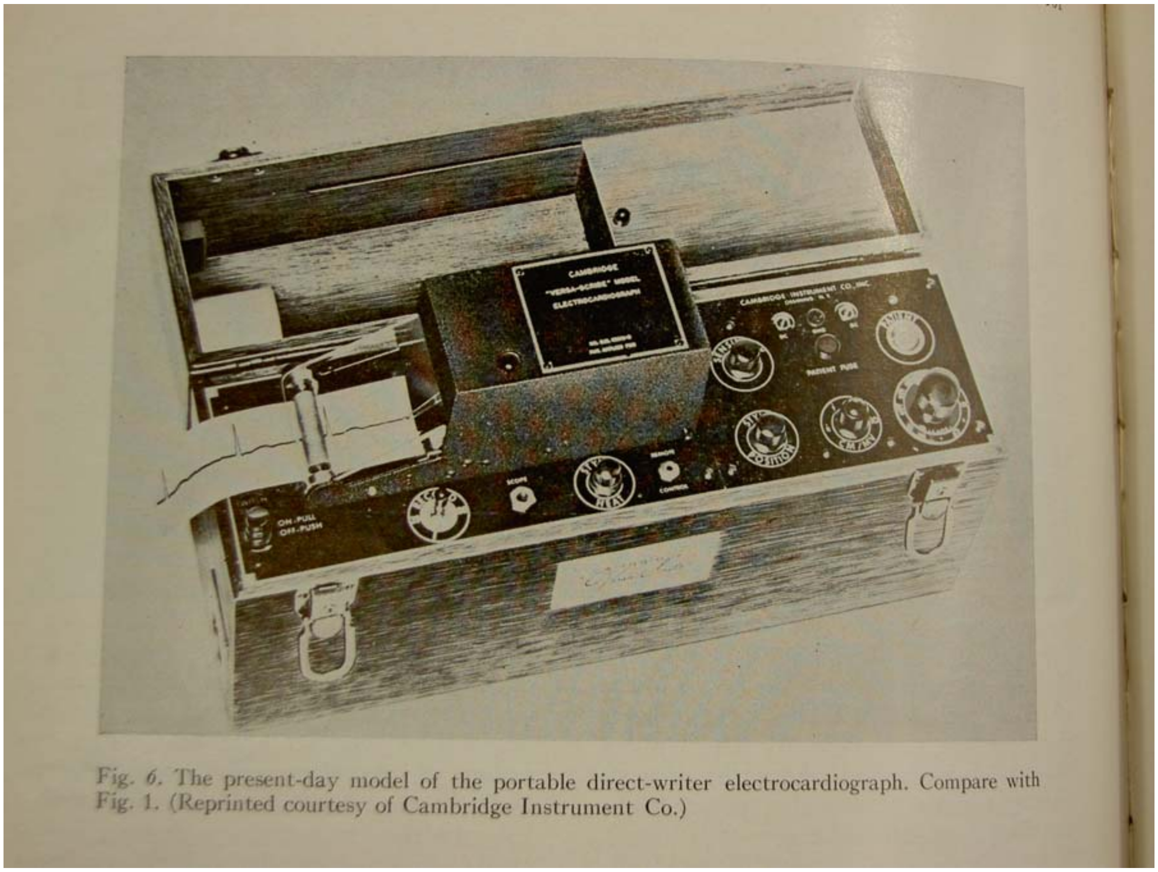

Fig. 6. The present-day model of the portable direct-writer electrocardiograph. Compare with Fig. 1. (Reprinted courtesy of Cambridge Instrument Co.)

Figure 12 - Standard strip chart EKG machine

Conclusions

Even in the early 1960s, vacuum tube electronics was the predominant technology. Transistorized equipment was not yet common, and especially for high voltages, tubes were used because transistors were still too fragile and too expensive.

Sir Adrian's final tribute to the valve amplifier and it's important role in the facilitation of electrophysiological research:

"When the academic scientist is forced to justify his existence to the man in the street he is inclined to do so by pointing out the essential part played by academic research in the development of our modern comforts. It is only fair, therefore, to point out that in this case the boot is on the other leg and the academic research has depended on the very modern comfort of broadcasting."

The development, and increasing use of equipment such as the valve amplifier altered not only the experimental design and possibilities, but also changed the whole ambience of the electrophysiological laboratory, which had, heretofore looked and sounded more like a boiler room than a laboratory.

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