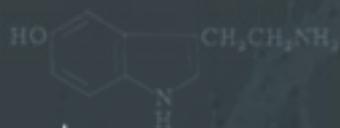




## The AMINCO-Bowman Spectrophotofluorometer



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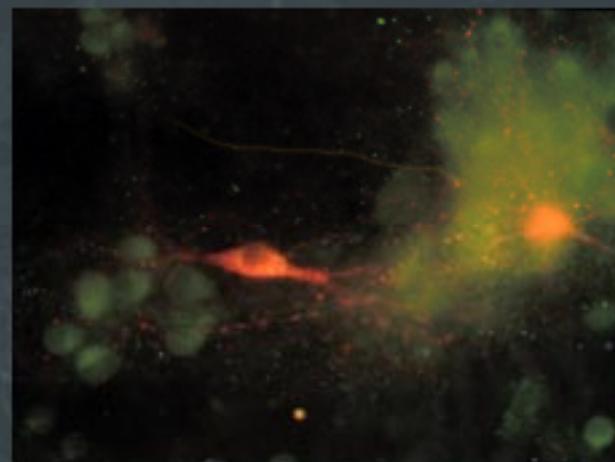
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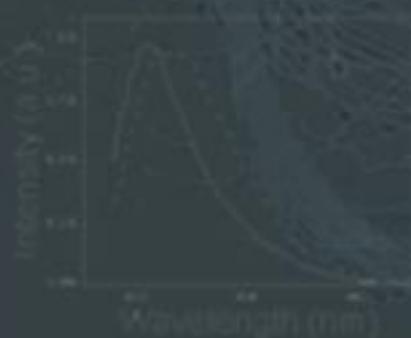
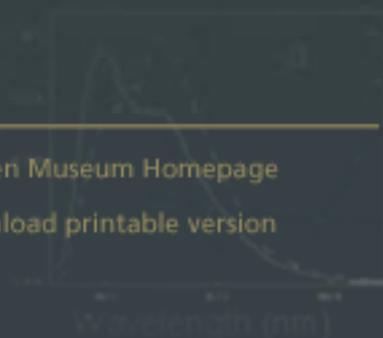
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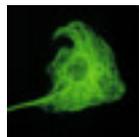
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▶ **begin the exhibit**

# The AMINCO-Bowman SPF

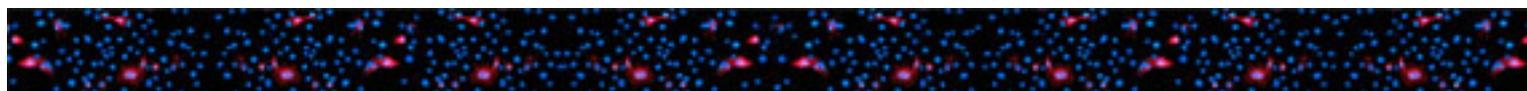


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**Fluorescence in medicine has enabled researchers to see the invisible.**



In the 1950s the NIH's Dr. Robert Bowman developed a sensitive instrument-called the spectrophotofluorometer, or "SPF"-that allowed scientists to use [fluorescence](#) as a way to identify and measure tiny amounts of substances in the body. This scientific breakthrough, invented almost half a century ago, is still used today in AIDS research and the Human Genome Project.



Spectrophotofluorometer



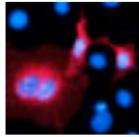
Dr. Robert Bowman

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# The AMINCO-Bowman SPF: History Section



## Fluorescence to the Rescue (1941-1945)

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## A desperate call to scientists and doctors: find a treatment for malaria!

The origins of the SPF lie in the antimalarial research of the 1940s. During World War II, the United States government issued a desperate call to scientists and doctors: find a treatment for malaria! Since Japan had taken over most of the world's supply of quinine—the best known treatment—Allied forces in the Pacific Theater needed a new drug, and fast.

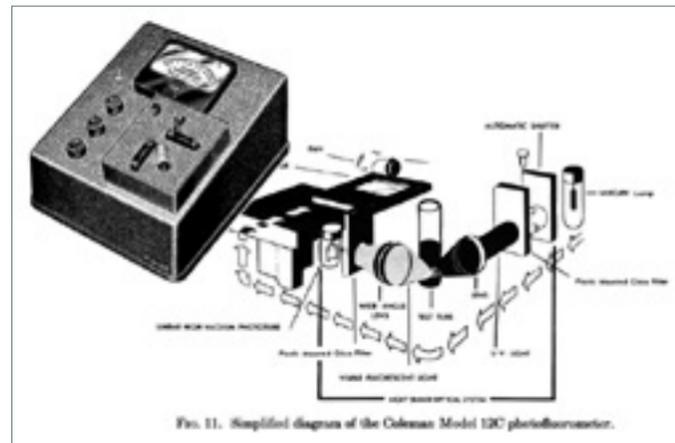
Led by [Dr. James Shannon](#), scientists at Goldwater Memorial Hospital in New York City and elsewhere tested thousands of drugs during the war. In many of the tests, doctors gave their subjects malarial fever, then injected the patients with a particular drug. They needed to make sure the drug reached the malarial parasites in the blood and learn how to adjust the dosages to avoid nasty side effects.

Using fluorescence, [Drs. Bernard Brodie](#) and [Sidney Udenfriend](#) of Goldwater developed a special test. They knew that many of the candidate drugs would fluoresce when excited by certain wavelengths of [ultraviolet \(UV\) light](#). With an instrument called a fluorometer, they could measure how much of the drug was in a patient's plasma sample by measuring the intensity of its glow. They thus found the critical level at which a promising drug, such as Atabrine, would attack the malaria-causing parasites without causing adverse side effects for the patient. Their results determined the standard dosage used by the U.S. armed forces as a preventative for malaria. The problem was that some candidate drugs did not fluoresce at the specific wavelengths available to them with their fluorometer, and therefore these drugs were undetectable in the plasma. The doctors could not use fluorescence as a way of "seeing," or measuring, these drugs in the body. There had been reports of fluorescence at other wavelengths, but at the time there were no commercially available sensitive UV fluorometers. Though they did come up with a treatment for malaria, the Goldwater scientists realized that their ideas reached beyond their tools. They needed a new type of instrument.



This photograph of the National Heart Institute Laboratory chiefs in the 1960s includes several members of the Goldwater group who worked with Dr. James A. Shannon.

**With an instrument called a fluorometer, they could measure how much of the drug was in a patient's plasma sample.**



The Coleman filter fluorometer.

**They needed a new type of instrument.**

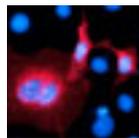
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In 1949 [Dr. James Shannon](#), leader of the antimalarial research effort at Goldwater, was named director of the laboratories and clinics of the newly created National Heart Institute (NHI) at the National Institutes of Health (NIH) in Bethesda, Maryland. He recruited researchers from Goldwater, including lab technician [Julius Axelrod](#) and [Drs. Bernard Brodie](#), [Sidney Udenfriend](#), [Robert Berliner](#), and [Robert Bowman](#).

Because of their interest in fluorescence in medicine that originated with antimalarial drug research, one of the group's early projects was the development of a new instrument that could help them learn more about how fluorescence could be utilized in scientific research.

## Dr. Robert Bowman of the Laboratory of Technical Development took the lead on the project in the early 1950s.

He was known for his talent in instrument-making, an indispensable skill in a research environment where scientists need good tools with which to test their theories and to lead them to new ideas.



The Laboratory of Technical Development at the National Heart Institute, early 1950s. Front row, left to right: Johnnie B. Langer, Hillary V. Trantham, Dr. Bert R. Boone, Robert E. Gorman, Patricia A. Caulfield. Back row, left to right: Dr. Harold J. Morowitz, Dr. Robert L. Bowman, Norman M. Garrahan, Dr. John L. Stephenson, Frank W. Noble.

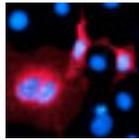
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## Anything Glows (1950-1955)

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NHI scientists did not yet know at which wavelengths many biological compounds would fluoresce. If the new instrument could emit light at wavelengths throughout the [ultraviolet](#) range, scientists might be able to excite fluorescence in compounds that could have interesting research applications. The question was, if they learned more about fluorescence, would this be useful in a practical as well as theoretical sense?

Working with others at NHI, Dr. Bowman developed the first prototype of his spectrophotofluorometer in 1955. Unlike previous fluorometers, this new instrument was able to vary the wavelength of exciting light as well as measure the intensity and wavelength of the emitted fluorescent light. This instrument could be used to survey biological compounds and help scientists figure out new ways to use fluorescence to study the body.

1. <u>Medical Heart Institute</u>		2. <u>Laboratory of Tissue Development</u>	
PROJECT TITLE		LABORATORY OF RESEARCH	
3. <u>Robert L. Bowman</u>		5. <u>100-10</u>	
PRINCIPAL INVESTIGATOR		SERIAL NO.	
6. <u>Development of Spectrophotofluorometry and Its Application to Biological Measurements</u>			
PROJECT TITLE			
7. <u>Dr. Sidney Udenfriend Laboratory of Chemical Pharmacology</u>			
Dr. E. Duggan - Guest Worker			
OTHER INVESTIGATORS			
9. <u>PROJECT DESCRIPTION</u>			
<u>Objectives:</u> (a) To make a practical spectrophotofluorometer capable of performing, as well or better than our experimental instrument available to other laboratories. (b) To continue to participate in exploring the histochemical-pharmacological applications of fluorescence determinations. (c) To continue to explore methods of eliciting and measuring fluorescence.			
<u>Methods Employed:</u> (a) The spectrophotofluorometer assembled in this Laboratory, being an experimental model was not a completed commercial design, so it was felt that a manufacturer of instruments could be interested in constructing a more practical form of this device. This would save this laboratory the expense and time of perfecting a practical model, and at the same time make such instruments available. The only company that affirmatively accepted our invitation was American Instrument Co., who, at present have completed their design. They are presenting the instrument to the Heart Institute for evaluation, and at the same time are entering into a production run of a number of these instruments. Our publication of the method and the publication of the method worked out on this instrument by the Laboratory of Chemical Pharmacology have already created a demand for a number of these instruments in many laboratories throughout the world.			
(b) In collaboration with the Laboratory of Chemical Pharmacology, methods of application to fluorometry and histochemical-pharmacological problems are being investigated. Materials of interest are being surveyed for histochemical fluorescence in the ultraviolet.			

NIH project description sheet for the "development of Spectrophotofluorometry and its application to biological measurements," 1955.

**If they learned more about fluorescence, would this be useful in a practical as well as theoretical sense?**

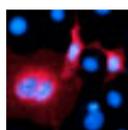
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Dr. Bowman had to improvise with his design. Authorized only to buy one expensive [monochromator](#), for example, he built the other one from parts he obtained from his contacts in the New York junk shop trade. One of his parts, a Steinheil quartz prism spectrograph, had been "liberated" from Germany during the war. He made his first prototype SPF with a mixture of used and new parts, including [diffraction gratings](#) and mirrors attached to a stone benchtop and "glued" in place with wax."

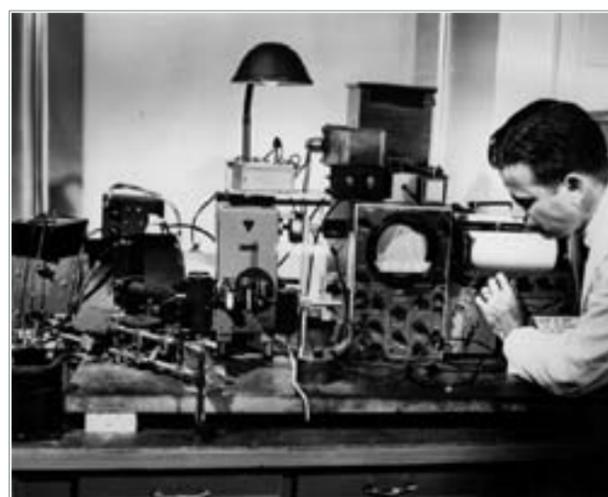
Because of exciting results with the prototype, the American Instrument Company (AMINCO) of nearby Silver Spring, Maryland, became interested in marketing the new instrument. The company assigned an engineer, Hugh Howerton, to collaborate with Dr. Bowman on a commercial version of the SPF-one that could be made without wax and war relics. The first AMINCO-Bowman SPF was exhibited at the 1956 Pittsburgh Analytical Instrument Conference.

In order to build interest in its product and promote research in the field of fluorescence, AMINCO funded a postdoctoral fellowship in fluorescence analysis for research at the National Heart Institute. The first AMINCO fellow, Dr. Daniel Duggan, studied hundreds of fluorescent compounds. His research convinced Dr. Bowman and AMINCO that they should proceed with the production of the SPF.

**He made his first prototype SPF with a mixture of used and new parts.**



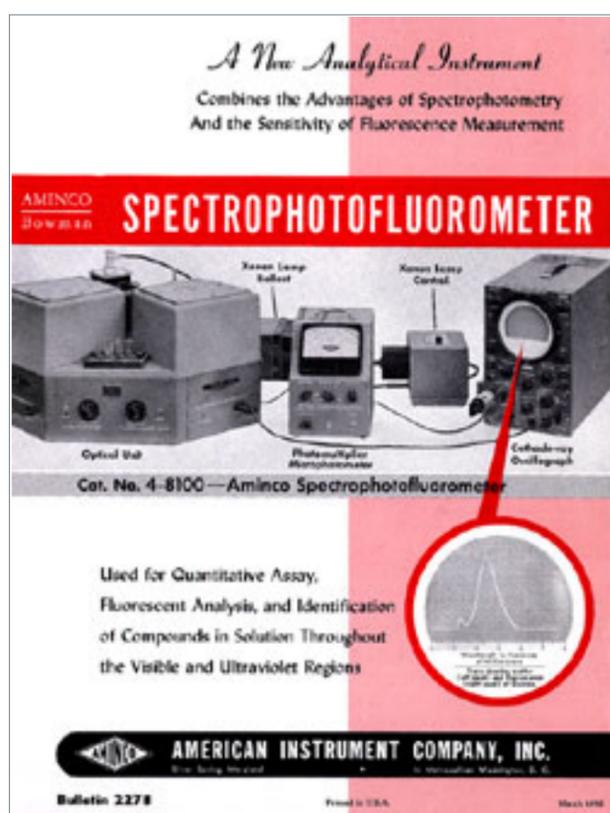
AMINCO engineer Hugh Howerton presenting a symposium about the SPF. Dr. Bowman is seated in the front row.



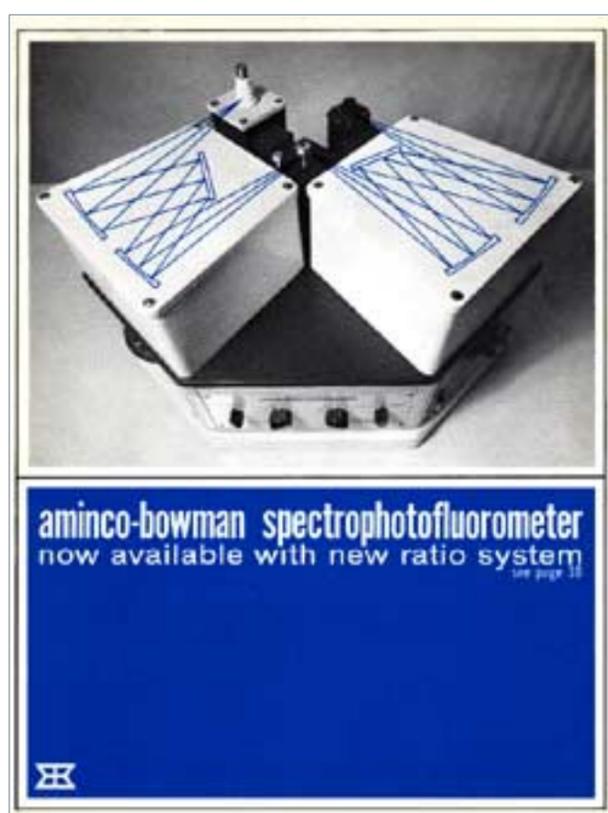
Dr. Daniel Duggan, a postdoctoral fellow at NHI, with the first laboratory prototype of the SPF.

## AMINCO sold out its initial run of twenty-five instruments

In the 1950s and 1960s, AMINCO marketed the SPF to the research field. Company sales representatives traveled across the country to train university faculty and other scientists how to use the instrument. The company even launched a newsletter called Fluorescence News. AMINCO sold out its initial run of twenty-five instruments, an impressive record in the tiny biomedical research market.



This Aminco sales bulletin from 1956 advertised "A New Analytical Instrument."



Aminco showcased new features of the SPF in this 1971 sales bulletin.

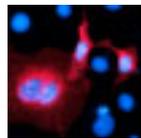
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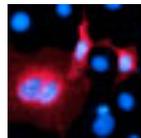
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Dr. Udenfriend used the SPF to test the fluorescence of different substances that would be of interest to biological scientists. To the amazement of the profession, he detected fluorescence in many molecules that had not been known to fluoresce! He and Dr. Bowman published a paper on the results of the early experiments with the SPF. Later, [Dr. Udenfriend](#) edited two volumes entitled *Fluorescence Assay in Biology and Medicine*. These works helped other scientists create new ways to use fluorescence in their own research.

**He detected fluorescence in many molecules that had not been known to fluoresce!**



The Nobel Prize Winner (1960s)

By 1955 [Dr. Julius Axelrod](#)-Dr. Brodie's former lab technician-had moved on to the National Institute of Mental Health (NIMH) and was working on his own experiments. He began using the new SPF in his research on what are now known as [neurotransmitters](#) in 1957.

**"The SPF . . . changed the direction of the whole field of neurobiology,"**

wrote Dr. Axelrod, looking back on his experience. He used the SPF to trace and measure tiny amounts of norepinephrine and serotonin in the brain. These neurotransmitters were present in the body in such minute amounts that no previously existing technology could have detected them. This research led to the development of antidepressant drugs such as Prozac. In 1970 Dr. Axelrod was awarded the Nobel Prize in Physiology or Medicine for his work with neurotransmitters.



Dr. Julius Axelrod, left, with Dr. Robert Bowman.

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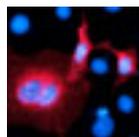
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## Fluorescence News (1970s-1990s)

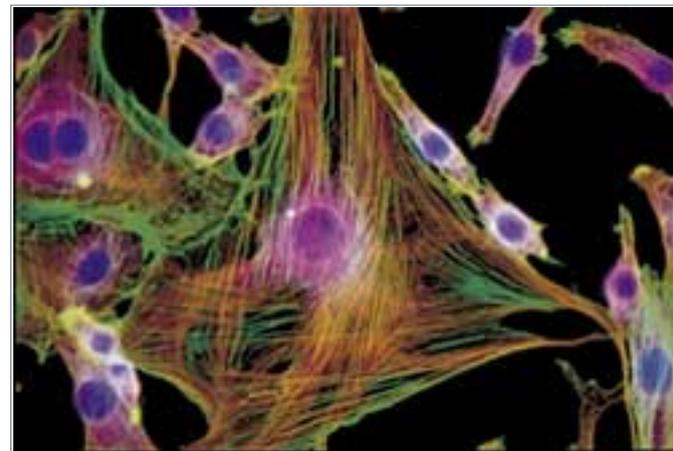
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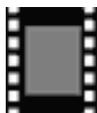
In the decades following [Dr. Axelrod's](#) groundbreaking work, many other scientists have used the SPF in their research. Dr. Bowman could never have imagined these applications back in 1955. He provided a tool for a new generation of scientists, who take the fluorescence phenomenon for granted and use variants of his instrument in their search for new ways to learn about the human body.

Today, fluorescence and updated versions of the SPF are used in measuring the quantity or cellular location of drugs, salts, proteins, or DNA. Other examples of research using fluorescence include: sequencing DNA; detecting viral or bacterial DNA during PCR (polymerase chain reaction) tests of potential bioterror samples; studying protein and drug activity and binding; measuring cell markers in AIDS; researching how muscles work; and tracing neuron receptors to map the brain.

**He provided a tool for a new generation of scientists.**



Photomicrograph of mouse fibroblast cells stained with three different dyes: two for different cytoskeletal components (green stain for actin fibers, orange for tubulin fibers), and one (violet) for the DNA coiled and packaged inside cell nuclei. Photograph by Jennifer Kramer and Sam Wells. Used with permission of Molecular Probes, Inc.



Click on the film icon to watch a video on the current uses of fluorescence and the SPF. The material in the video is also available in text-only format.

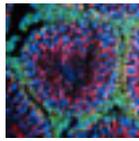
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# The AMINCO-Bowman SPF: Science Section

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## The Spectro-Photo-Fluorometer

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## The three parts of the Spectro-Photo-Fluorometer:



### Spectrometer

A spectrometer shines a light on a sample and measures how much light is absorbed at a specific wavelength. Knowing how much light is absorbed can help scientists identify the substances in a given sample, since each substance absorbs a different amount of light at different wavelengths. Spectrophotometers usually have a photomultiplier tube that amplifies the signal for accurate measurement.

**A spectrometer shines a light on a sample and measures how much light is absorbed at a specific wavelength.**

Here is how it works: first, a bright light source is used to create light of a known wavelength and intensity. The light passes through a monochromator, which filters out all except a narrow band of wavelengths (or colors) which will be used to illuminate the sample. This narrow band of light is passed through the sample material where some is absorbed. The remaining light that passes through the sample strikes the light-sensitive detector. The detector generates an electrical signal in proportion to the light intensity. The electrical signal is amplified and read out on a meter or other device.

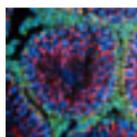
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## The purpose of a photomultiplier tube (PMT) is to measure very weak light.

### Photomultiplier tube

The purpose of a photomultiplier tube (PMT) is to measure very weak light. The tube multiplies the effect of the light that strikes it and converts photons of light into electrical signals so that the light can be precisely measured.

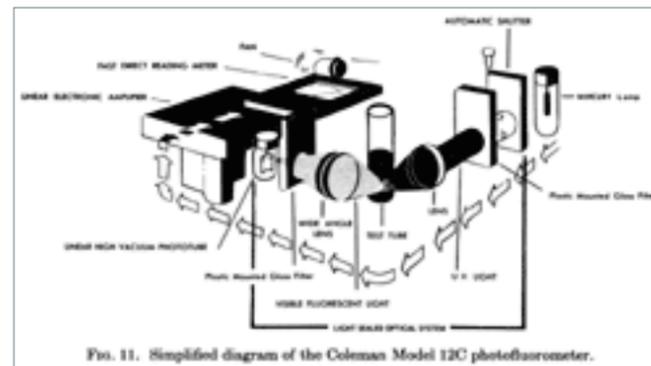
Each photon (bit of light) strikes a photocathode, ejecting an [electron](#). The electrons are accelerated toward a secondary electrode called a dynode, which is held at a more positive potential so that each electron gains enough energy to eject several electrons from the dynode. This is the electron "multiplier." By using a series of dynodes, the PMT creates a cascading effect-the system creates 100,000-10,000,000 electrons for each photon hitting the first cathode. The amplified signal can be collected and measured at the end.

### Fluorometer

A fluorometer measures the intensity of fluorescing molecules in a sample of blood or body tissue. Individual molecules are too small to be seen. However, when hit with ultraviolet light, these same materials can be seen with a fluorometer, because now the substances fluoresce, or glow. Scientists can use the fluorescent properties to see things that are otherwise too small to be visible.

The fluorometer measures the amount of fluorescent radiation produced by a sample when the sample is exposed to monochromatic light. Light focuses in on the [cuvette](#). In early fluorometers, fluorescent light entered the vacuum phototube through the secondary filter at right angles to the exciting light. The photocurrent is recorded by an electric amplifier connected to a galvanometer, which detects and measures a small electric current by movements of a magnetic needle of coil in a magnetic field.

## A fluorometer measures the intensity of fluorescing molecules in a sample of blood or body tissue.



The Coleman filter fluorometer measures the total fluorescence emitted by all materials in a sample.

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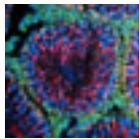


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**This research tool combines the technologies of the spectrometer, the photomultiplier tube, and the fluorometer to provide sensitive measurements of the color spread, or spectrum, of fluorescent light in a sample.**

### Spectrophotofluorometer

This research tool combines the technologies of the spectrometer, the photomultiplier tube, and the fluorometer to provide sensitive measurements of the color spread, or spectrum, of fluorescent light in a sample. The instrument counts the amount of light given off in each color band and can be used to trace and measure tiny components of a sample of blood, body tissue, or other substance.

The early AMINCO-Bowman SPF used two monochromators, one to isolate a narrow band of light for excitation and the other at right angles to the first to analyze the emitted fluorescence by measuring the intensity of the fluorescent light vs. wavelength. For its excitation energy, the SPF used a [xenon-arc lamp](#), which emitted a range of white light emission from the visible well into the ultraviolet.



Spectrophotofluorometer

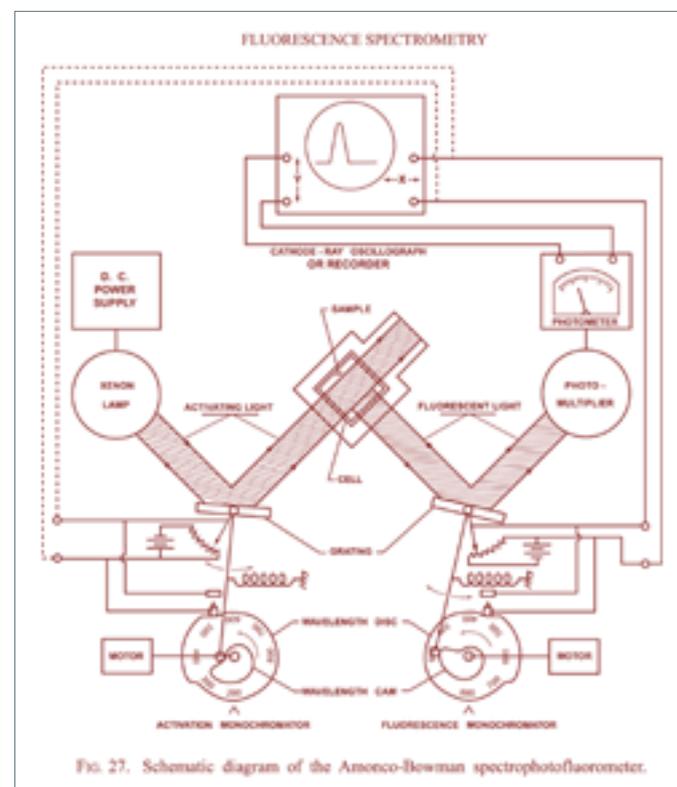
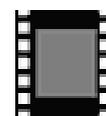


Diagram of the spectrophotofluorometer.



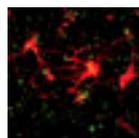
Click on the film icon to watch an informative video about the operation of the SPF. The material in the video is also available in text-only format.

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# The AMINCO-Bowman SPF: Scientific Glossary



## Scientific Glossary

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#### Arc Lamp

An arc lamp is an optical source used in many kinds of instruments to provide high levels of brightness. Arc lamps are often filled with gases, such as krypton, mercury, or xenon. Developed in Germany during World War II for use in high-powered search lights, the particularly bright and penetrating xenon arc lamps are now used in both SPFs and IMAX theaters.

#### Assaying

Assaying is the process of determining how much of a certain substance is present.

#### Cuvette

A cuvette is a small transparent tube (often rectangular) that holds a solution or a sample.

#### Diffraction gratings

Diffraction gratings are closely spaced, straight, parallel grooves on an aluminum surface which are able to separate (or diffract) white light into its component wavelengths. By the early 1950s they were rare but available, so Dr. Bowman was able to use one in his prototype SPF.

#### Electron

An electron is a negatively charged subatomic particle.



#### Fluorescence

Fluorescence is the glow made by some materials when they are "excited by" (react to) light in the visible or invisible (ultraviolet) range. Molecules absorb photons (the smallest possible bits of light) at one wavelength of color and become excited. The molecules change slightly as they store the energy of the photons. As they change, they leak some of the energy to surrounding molecules. Using the remaining energy, the molecules emit new photons in different colors. This creates a fluorescent glow. **(Click on film icon to watch an animation on the physics of fluorescence).**

#### Monochromator

A monochromator selects light from a narrow band of wavelengths using either a prism or a diffraction grating. High quality but very expensive monochromators were just beginning to be produced in the United States in the 1950s when Dr. Bowman used them in his instrument.

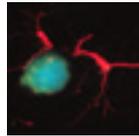
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# The AMINCO-Bowman SPF: Biography Section

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## Julius Axelrod (1912- )

Julius "Julie" Axelrod won the Nobel Prize in 1970 for neurotransmitter research conducted in part with the spectrophotofluorometer (SPF). Dr. Axelrod was born in 1912 in New York City and attended the College of the City of New York. After graduation he worked as a lab assistant and a research chemist. He then moved on to Goldwater Memorial Hospital, where he worked as Dr. Brodie's lab technician for many years. In 1949 both Axelrod and Brodie joined the newly formed National Heart Institute (NHI) and while at NHI Axelrod earned his doctoral degree at George Washington University.

In 1955, after completing his doctoral work, Dr. Axelrod became chief of the Section on Pharmacology at the Laboratory of Clinical Science at the National Institute of Mental Health (NIMH) and began using the new SPF in his research on neurotransmitters. With the SPF, he was able to measure tiny amounts of neurotransmitters in the brain. He studied norepinephrine and described the process for storage, release, and "re-uptake" by the cells as needed. For this work, he was awarded the 1970 Nobel Prize in Physiology or Medicine. Dr. Axelrod formally retired from NIMH in 1984, though he continued to keep up a laboratory and be active in NIH research.



Dr. Julius Axelrod.

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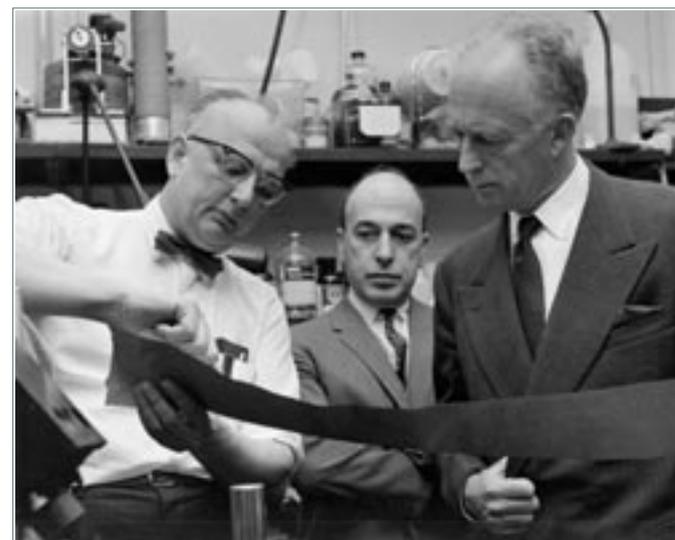
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### Acknowledgements

Robert Berliner is an eminent renal physiologist who was part of Dr. Shannon's group at Goldwater Memorial Hospital during World War II and came to NIH after the war. Dr. Berliner, born in New York City in 1915, earned his B.S. degree from Yale and his M.D. from Columbia in 1939. He served his medical school residency at Goldwater Memorial Hospital and moved to the National Heart Institute in 1950.

Dr. Berliner was chief of the Laboratory of Kidney and Electrolyte Metabolism at NHI for twelve years (1950-1962). He also served as the director for intramural research for that institute and in 1968 was named director of Laboratories and Clinics at NIH. He accepted an appointment as the first deputy director for science at NIH in 1969, a post he kept until he left NIH to become dean of the Yale University School of Medicine in 1973. Dr. Berliner, who studies the control of the excretion of sodium and potassium salts in the kidney, remains on the Yale faculty as an emeritus professor of cellular and molecular physiology.



Robert Berliner (center) looks on as Robert Bowman (left) discusses his research with an AMINCO representative.

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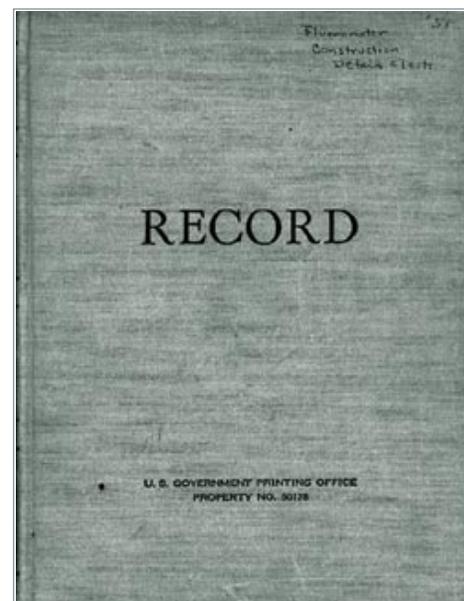
**References Links**

**Acknowledgements**

Dr. Robert L. Bowman invented the practical spectrophotofluorometer (SPF). Born in New York City in 1916, Bowman tinkered with crystal radio sets, cameras, spare parts, and chemicals as a youth. He received his M.D. degree from the New York University College of Medicine in 1942 and went on to serve in the U.S. Army Medical Corps during World War II. After the war he returned to New York to work at Goldwater Memorial Hospital.

When James Shannon of Goldwater was named the head of the new National Heart Institute (NHI), Bowman—newly discharged from the Army—joined him and moved on to the Laboratory of Technical Development at the National Heart Institute. There he worked with Drs. Brodie, Berliner, Udenfriend, and others to develop the SPF.

During his career at NHI, Dr. Bowman worked with other scientists to develop instruments that would help them do their research. Trained as a doctor and possessing a special knack for instrument manufacture, Dr. Bowman had an unusual mixture of talents and was honored with many awards including the 1967 American Chemical Society award in chemical instrumentation.



Click on notebook to flip through the pages of Dr. Bowman's laboratory notebook.



Dr. Bowman receiving the 1967 American Chemical Society award in chemical instrumentation.



Bowman won the American Chemical Society Award in 1967.

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### Acknowledgements

Dr. Bernard B. "Steve" Brodie was an internationally renowned pharmacologist whose groundbreaking work at Goldwater and NIH—including his involvement in the development of Tylenol—earned him many honors. Dr. Brodie attended McGill University in Montreal and then studied organic chemistry at New York University. He came to Goldwater Memorial Hospital to work with Dr. James Shannon's antimalarial group during World War II. His important publications in the 1940s helped lay the groundwork for the future study of drug metabolism.

As head of the Laboratory for Clinical Pharmacology at NIH after the war, Dr. Brodie worked with and trained a group of scientists who would become the leaders in the science of drug metabolism. Their work was accompanied by increased research into instrumentation and technology, including the spectrophotofluorometer. Dr. Brodie won the Lasker Award, often considered the American Nobel Prize, in 1967. The award cited his "extraordinary contributions to biochemical pharmacology."



Bernard "Steve" Brodie

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Dr. James Shannon, leader of the Goldwater antimalarial research group, served as director of NIH from 1955-1968. Shannon, born in 1904, was educated in New York City and received his M.D. from the New York University School of Medicine in 1929. After serving his residency at Bellvue Hospital, Shannon returned to NYU to study for the Ph.D. in Physiology, which he earned in 1935. He spent the next fifteen years on the faculty of the NYU School of Medicine, where he studied the relatively new field of kidney physiology.

In 1941 Shannon took responsibility for directing the NYU Research Service at the new Goldwater Memorial Hospital at Welfare (now Roosevelt) Island in New York. However, his plans to study renal physiology there were interrupted by the government's call for research into antimalarial drugs. He assembled a group of doctors responsible for recommending an appropriate dosage of Atabrine. They also developed Chloroquine, the drug of choice to treat malaria for several subsequent decades. After the war, Shannon was named director of a pharmaceutical company before becoming an associate director in charge of research at the newly created [National Heart Institute](#) at NIH.

In 1955 Shannon was named director of NIH, a post he held for thirteen years. He oversaw a period of vastly increased construction, increased funding for research personnel and laboratories, and the creation of new research centers. Shannon brought money from Capitol Hill and new optimism to NIH, from which he retired at the mandatory age of sixty-four in 1968. Shannon then served in a variety of consultant and board positions with various universities, hospitals, and other institutions. To honor him for his many contributions to NIH, the central administration building (Building 1) was named for him in 1983.



James Shannon

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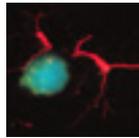


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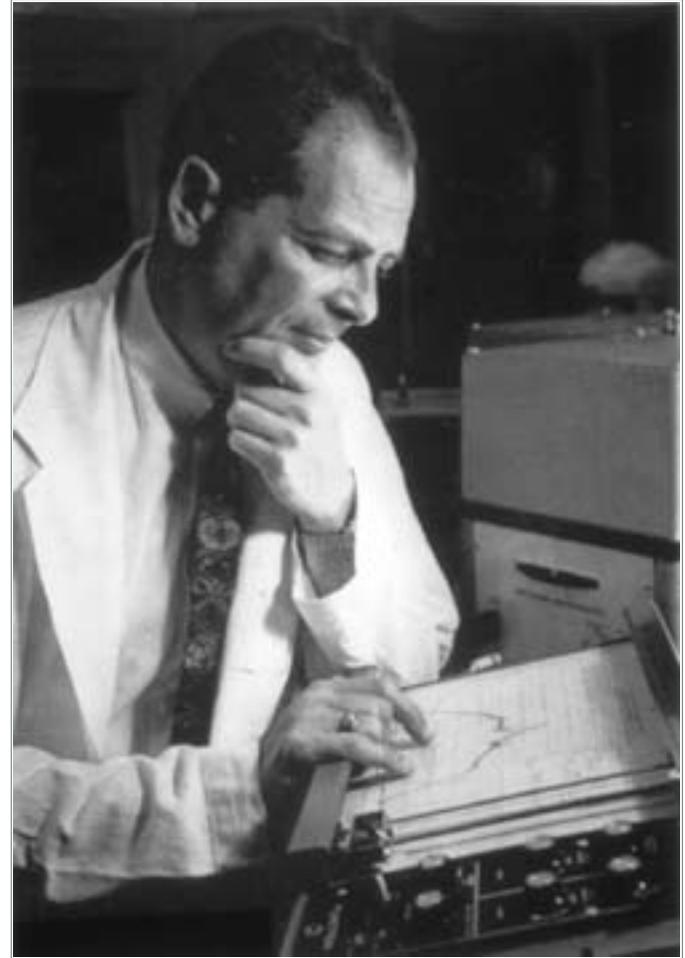
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## Sidney Udenfriend (1918- 2001)

Dr. Sidney Udenfriend, a member of the Goldwater antimalarial group, subsequently worked with Dr. Bowman at the National Heart Institute (NHI) and analyzed and catalogued substances using the spectrophotofluorometer (SPF). Udenfriend had earned his master's degree at New York University (NYU) when he joined the Goldwater group in 1942. He and Dr. Brodie developed the special test with the photofluorometer to screen and test antimalarial drugs during World War II. After the war, Udenfriend returned to graduate school at NYU to finish his doctorate. Dr. Udenfriend came to work at the NHI in 1950 at Dr. Shannon's invitation, following a postdoctoral fellowship at Washington University in St. Louis. At NHI he helped his colleague Robert Bowman develop the SPF.

Dr. Udenfriend left NIH for private industry in 1967 to become the founding director of the Roche Institute of Molecular Biology (RIMB), a position he held until 1983. Formerly located in Nutley, New Jersey, RIMB was originally staffed by many of Udenfriend's former colleagues from Dr. Brodie's lab at NIH. When RIMB closed its Nutley laboratories in 1995, Dr. Udenfriend, who still maintained an active lab there until the closure, called the institute "the envy of scientists around the world, a camelot of the biological sciences."



Sidney Udenfriend

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In 1995 Dr. Sidney Udenfriend wrote a history of the SPF, "Development of the Spectrophotofluorometer and its Commercialization."

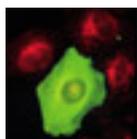
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## After the 1950s, the SPF gave rise to many new uses for fluorescence in medical research.

American doctors and scientists began investigating the uses of fluorescence in medicine in the 1920s and 1930s. In the 1940s, then, when working with antimalarial drugs, the Goldwater group already knew that Atabrine and other drugs fluoresced at certain [ultraviolet](#) wavelengths just outside the visible range.

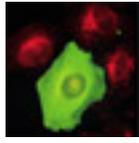
Indeed, other organic, or carbon-containing, compounds also fluoresce when irradiated by a light of the correct wavelength. After the 1950s, the SPF gave rise to many new uses for fluorescence in medical research. Today, fluorescence microscopes use sensitive electronic cameras to observe directly in three dimensions how cells function. Recently, advances in pulsed lasers have provided selective excitation of fluorescence in many tiny regions inside living cells and the ability to detect events lasting less than a trillionth of a second in proteins. Hundreds of new fluorescent dyes are available to light up specific targets, and fluorescent-activated cell sorters can be used to separate white blood cells from other cells found in blood. Using fluorescence might yield surprising new results in the future of medicine.

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## Malaria

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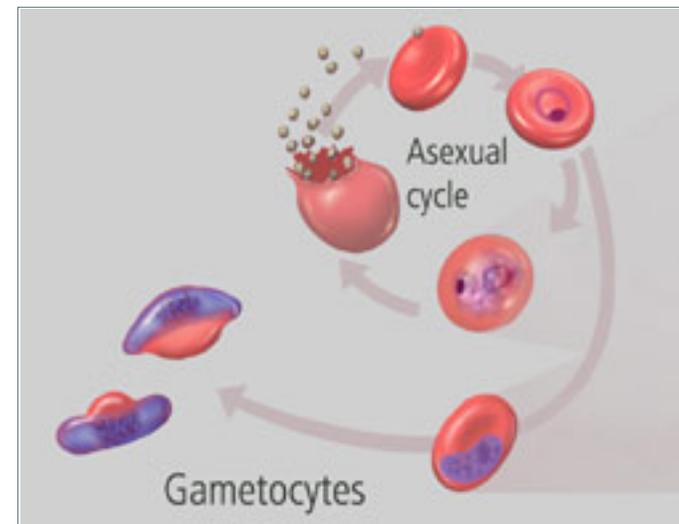
**Acknowledgements**

**At the time, malaria killed close to 3 million people each year and infected millions more.**

In March 1942 the Japanese army took control of the Dutch East Indies (Indonesia). In doing so, they cut off the rest of the world's supply of the malaria treatment quinine, harvested for hundreds of years from the bark of the Chinchona tree. At the time, malaria killed close to 3 million people each year and infected millions more. The disease was debilitating to U.S. Army forces in tropical regions. The United States government responded by developing a major program to develop new drugs. Through dozens of universities, hospitals, and laboratories the government tested close to 15,000 potential compounds during the war. Government doctors used federal and state prisoners as well as lab animals such as ducks, dogs, and canaries for their tests. Syphilis patients, for whom malarial fever served as a cure, were a major source of experimental subjects.

Malaria is caused by a parasite that gets into the red blood cells and multiplies, causing the cells to rupture and the body to respond with a fever. For an antimalarial to work, it must intercept the parasite's life cycle by reaching the parasite in the patient's blood. The drug has to build up in the patient's blood until it has killed all the trouble-causing parasites.

By the spring of 1943, doctors at Goldwater had presented the army with new dosage rules for Atabrine, which had already been used in the place of quinine but with previously poor results. They also developed new drugs such as Chloroquine. Used for several decades, Chloroquine has been largely replaced by new drug compounds because the malarial parasites in regions such as Southeast Asia, portions of South America, and much of Africa became resistant to the drug. Organizations such as Roll Back Malaria and the Medicines for Malaria Venture, co-sponsored by several public and private international groups, fund research into new drugs for especially resistant areas.



Click on the image above to see the life cycle of the malaria parasite in the human body. Image courtesy of the Medical Arts and Photography Branch, NIH.

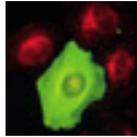
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## Atabrine and the New Pharmacology

The focus of the Goldwater group's antimalarial research was on American Atabrine, a synthetic antimalarial first developed in Germany in the 1930s. Though scientists in the United States had synthesized the drug within a few years, troops did not usually take their medicine. The Atabrine turned them yellow, made them sick, and seemed to take forever to work. What was the problem?

### Drs. Brodie and Udenfriend figured out how to measure Atabrine levels in the blood using fluorescence.

**Dosage.** Army doctors dispensed the Atabrine at the same dose levels they had used for quinine. In the 1940s, however, a new method of dose-setting was coming into vogue, and one of the biggest proponents of what was called the "New Pharmacology" was Dr. James Shannon. At Goldwater, he put Drs. Brodie and Udenfriend on the problem of re-setting the dosage for Atabrine, using this new approach.

First, the scientists had to find a way to measure the concentration of the drug in the blood. Second, they had to figure out what blood concentration would yield the desired result. And third, they had to set a dosage schedule to maintain that desired blood level.

Drs. Brodie and Udenfriend figured out how to measure Atabrine levels in the blood using fluorescence. Since Atabrine fluoresced at a certain wavelength, all they had to do was take a sample of blood [plasma](#) from a malarial patient who had taken Atabrine. When seen through a fluorometer, the plasma would "glow" at a level proportional to the amount of Atabrine in the sample.

The scientists found that, at the current dosage, the Atabrine was soaked up in muscle fiber and the liver, causing uncomfortable side effects before it was able to build up in the blood. By changing the dosage-to a first-day big dose to saturate the tissues followed by small daily doses that would then go right to the blood-the Goldwater group was able to save Atabrine, as well as millions of American troops abroad.

Dr. Shannon's so-called "gospel of blood levels" revealed the central importance to pharmacology of being able to measure the concentrations of drugs in the blood. This central issue led the Goldwater team to be interested in a more sensitive instrument than the fluorometer they had used during the war, and therefore led to the development of the SPF.

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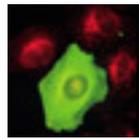
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## SSRI Research

NIH scientist Dr. Julius Axelrod used the SPF to measure tiny amounts of serotonin in the blood. Serotonin was first isolated from the blood in 1948 and identified as being present in the central nervous system. The body system involving serotonin is known to affect mood, emotion, sleep, and appetite. One cause of depression is an abnormal function of the serotonin transmitter system. Therefore, a drug that builds the concentrations of serotonin should alleviate the symptoms.

**Dr. Axelrod's research, for which he won the Nobel Prize in 1970, led to the development of SSRI (selective serotonin re-uptake inhibitor) drugs such as Prozac, Zoloft, and Paxil.**

### How does an SSRI work?

The brain is made up of neurons, which are interconnected brain cells. Messages travel along these cells. When a message reaches the end of a neuron, it has to jump a gap (called a synapse) to the next one. To do this, the neuron releases tiny amounts of a chemical (a neurotransmitter) into the gap between the nerve cells. Ideally, a nerve impulse starts in the new nerve, and thus the message gets from one nerve to the next. In order for the original nerve to recover and get the next message, it needs to replace its stocks of the neurotransmitter in the original neuron so it is ready to send the next message. The "healthy" body thus takes the neurotransmitter back into the originating neuron (this is called "re-uptake").

In the case of depression, certain neurotransmitters such as serotonin are lacking, so they cannot be taken back in full to the originating neuron and therefore cannot send the next message. SSRIs slow down the process of returning serotonin to the end of the neuron it comes from (they inhibit the process of re-uptake). This makes it more likely that enough serotonin will build up to set off the impulse in the next neuron. Therefore, SSRIs work by allowing the body to make the best use of reduced amounts of serotonin.

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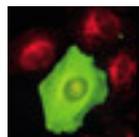
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**During the war, in the basement of Goldwater's Building D, were assembled what has been called "the workings of elite science"-the scientists who would go on to develop many of the great biomedical research advances in the postwar era.**

Goldwater Memorial Hospital in New York was the focus of antimalarial drug research during World War II. Dr. James A. Shannon led the group, which included Drs. Bernard Brodie, Sidney Udenfriend, and Robert Berliner, and future Nobel Prize winner Julius Axelrod. Dr. Robert Bowman came to Goldwater after the war.

Goldwater Memorial Hospital opened in 1939 as the first public hospital in America devoted solely to the treatment of chronic diseases. In 1942 it became the focal point for a national campaign to develop a new treatment for malaria-one of the most significant medical problems for the Allies in World War II. During the war, in the basement of Goldwater's Building D, were assembled what has been called "the workings of elite science"-the scientists who would go on to develop many of the great biomedical research advances in the postwar era.

After the war, though the antimalarial group had moved, for the most part, to NIH, Goldwater itself continued to be the locus for research into chronic disease. Goldwater, which was named after S. S. Goldwater, a New York hospital commissioner, merged with the Bird S. Coler Hospital in 1996. The 2,000-bed long-term health facility provides extended care for people who need ongoing medical attention due to diseases including Alzheimer's and AIDS.

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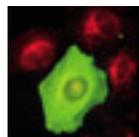


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 1969-1976 National Heart & Lung Institute  
 1976-Present National Heart, Lung, and Blood Institute

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The National Heart Institute (NHI), one of the NIH's first institutes, was founded on June 16, 1948, to develop expertise in heart disease research and cardiovascular disease. The institute transfers basic science knowledge to physicians in the hopes of fighting diseases. In 1949 [Dr. Shannon](#) became director of the laboratories and clinics of the newly created NHI. He recruited many of his best researchers from Goldwater, including [Drs. Bowman](#), [Brodie](#), [Udenfriend](#), and [Berliner](#).

The National Heart Institute fostered collaboration among researchers, doctors, and scientists. Ideally, such interaction could accelerate the transfer of basic science knowledge to practicing physicians for the patient's benefit. A key component in this process was the Laboratory of Technical Development, where Dr. Bowman did his research.

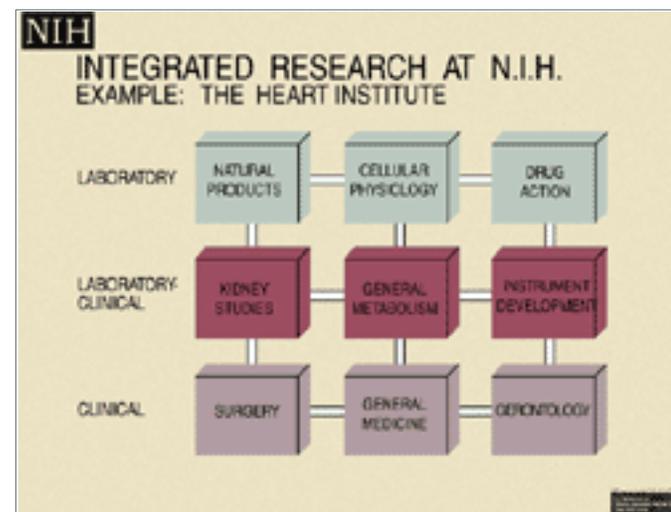


Chart from NIH Databook, 1954.

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## Introduction

Robert L. Bowman, "The History and Development of the Spectrophotofluorometer," *Fluorescence News* 8 (1974): 1-8.

## History Section

R. L. Bowman, P. A. Caulfield, and Sidney Udenfriend, "Spectrophotofluorometric Assay in the Visible and Ultraviolet," *Science* (1955): 32-33.

## Science Section

Sidney Udenfriend, "Development of the Spectrophotofluorometer and Its Commercialization," *Protein Science* 4 (1995): 542-55.

## Scientific Glossary

Robert Kanigel, *Apprentice to Genius: The Making of a Scientific Discovery* (Baltimore: The Johns Hopkins University Press, 1986).

This book discusses the mentor-student relationship in the sciences, focusing on the chain between Bernard Brodie, Julius Axelrod, Solomon Snyder, and Candace Pert. It includes information about the Goldwater antimalarial group and NIH in the 1950s and 1960s.

## Biography Section

Robert L. Bowman's papers are held at the Stetten Museum, National Institutes of Health, Bethesda, Maryland.

## Special Spotlights

James Shannon's papers are held at the National Library of Medicine, including correspondence, talks, articles, reports, and photographs.

Julius Axelrod's papers are held at the National Library of Medicine, including lab notebooks, research reports, correspondence, speeches, and photographs.

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<http://www.nobel.se/medicine/index.html>

The Nobel e-museum includes biographical information on Nobel Laureates in every field, including Julius Axelrod (1970).

### History Section

<http://profiles.nlm.nih.gov/HH/>

The National Library of Medicine's Profiles in Science web site includes biographical information on Julius Axelrod, as well as scanned papers and photographs.

### Science Section

<http://www.nap.edu/readingroom/books/biomems/jshannon.html>

The National Academy Press web site includes this biographical essay on James Shannon, former NIH president.

### Scientific Glossary

[http://www.laskerfoundation.org/index\\_flash.html](http://www.laskerfoundation.org/index_flash.html)

The web site of the Albert Lasker Foundation includes information about the prize and about each winner. Dr. Brodie won the Lasker in 1967.

### Biography Section

<http://www.pittcon.org>

The AMINCO-Bowman SPF was first exhibited at the 1956 Pittsburgh Analytical Conference. Today the Pittsburgh Conference and Exposition on Analytical Chemistry and Applied Spectroscopy continues to attract the latest advances in science instrumentation.

### Special Spotlights

<http://www.nih.gov/od/museum/exhibits/history/>

This on-line exhibit from the Stetten Museum provides "A short history of the National Institutes of Health."

### References Links

[http://www.who.int/health\\_topics/malaria.htm](http://www.who.int/health_topics/malaria.htm)

<http://www.cdc.gov/travel/malinfo.htm>

These sites contain information on research and treatment of malaria from the National Institute of Allergy and Infectious Diseases (at NIH), the World Health Organization, and the Centers for Disease Control.

### Acknowledgements

<http://www.nhlbi.nih.gov/index.htm>

The web site of the National Heart, Lung and Blood Institute (formerly the National Heart Institute) of the NIH provides information about current research.

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## Acknowledgements

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