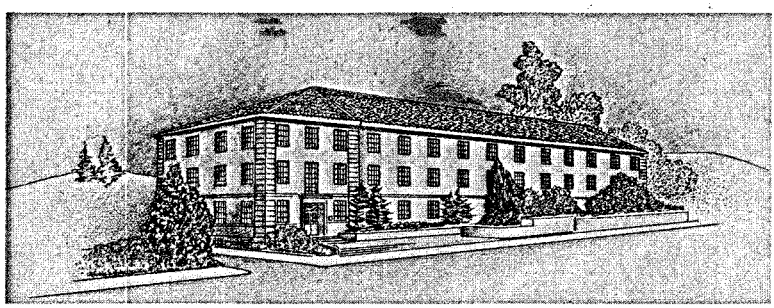
Fifty Years of Progress 1937–1987



Donner Laboratory

Division of Biology and Medicine of the Lawrence Berkeley Laboratory

University of California Berkeley, CA

DISCLAIMER

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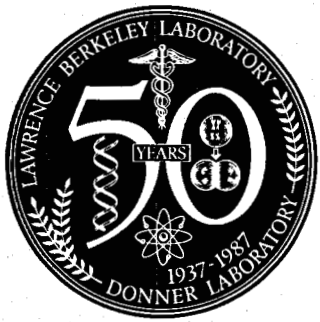
Fifty Years of Progress
1937–1987



Donner Laboratory
Division of Biology and Medicine
of the
Lawrence Berkeley Laboratory

University of California
Berkeley

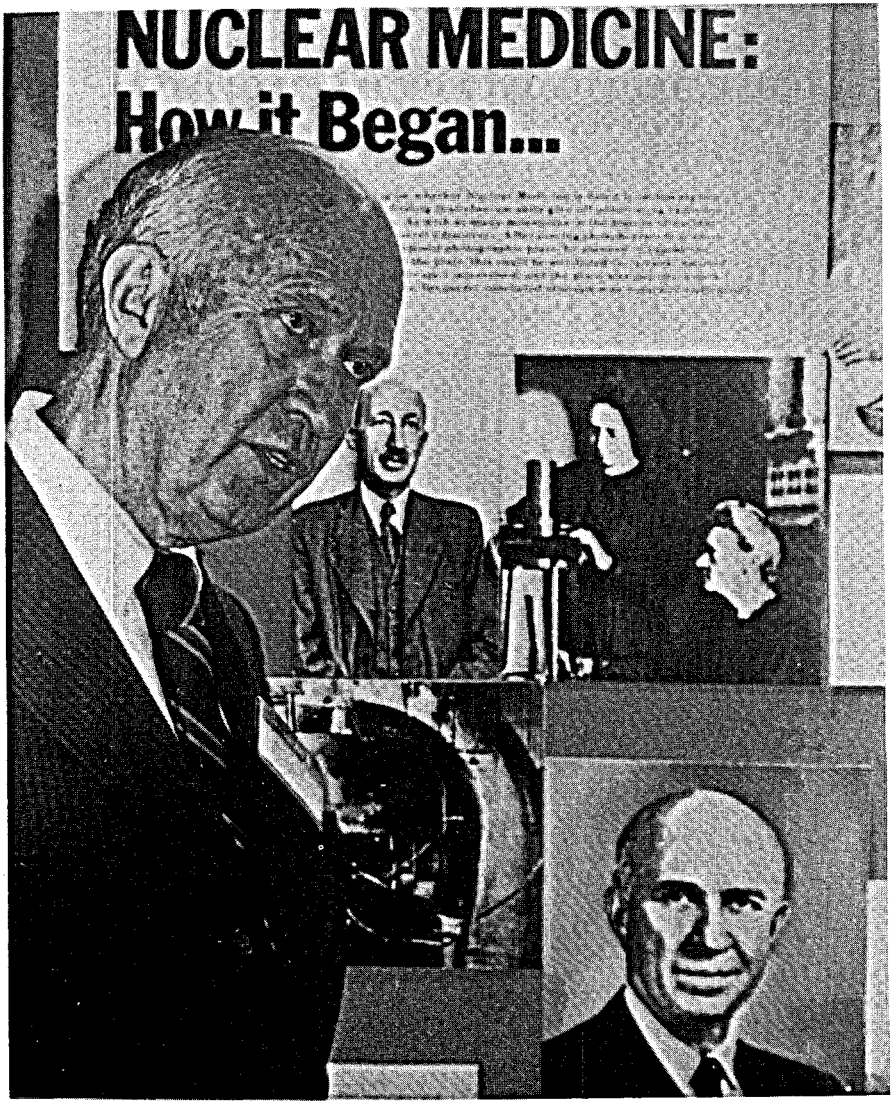
Preface

This booklet was prepared for the 50th anniversary of medical and biological research at the Donner Laboratory and the Lawrence Berkeley Laboratory of the University of California. The intent is to present historical facts and to highlight important facets of fifty years of accomplishments in medical and biological sciences. A list of selected scientific publications from 1937 to 1960 is included to demonstrate the character and lasting importance of early pioneering work.

Dr. William Myers, Dr. Patricia Durbin and Ms. Jan DeMoor provided much of the historical material. Julie Twitchell, Ralph Dennis, and Loretta Lizama assisted in the technical production. The organizational concept is to show the research themes starting with the history, then discoveries of medically important radionuclides, then the use of accelerated charged particles in therapy, next human physiology studies then sequentially studies of biology from tissues to macromolecules; and finally studies of the genetic code.

Unfortunately, space and time did not permit us to acknowledge all the great scientists and represent accurately their contributions in this booklet. We hope the information in this booklet will further inform and inspire our colleagues and students.

Thomas F. Budinger
Editor



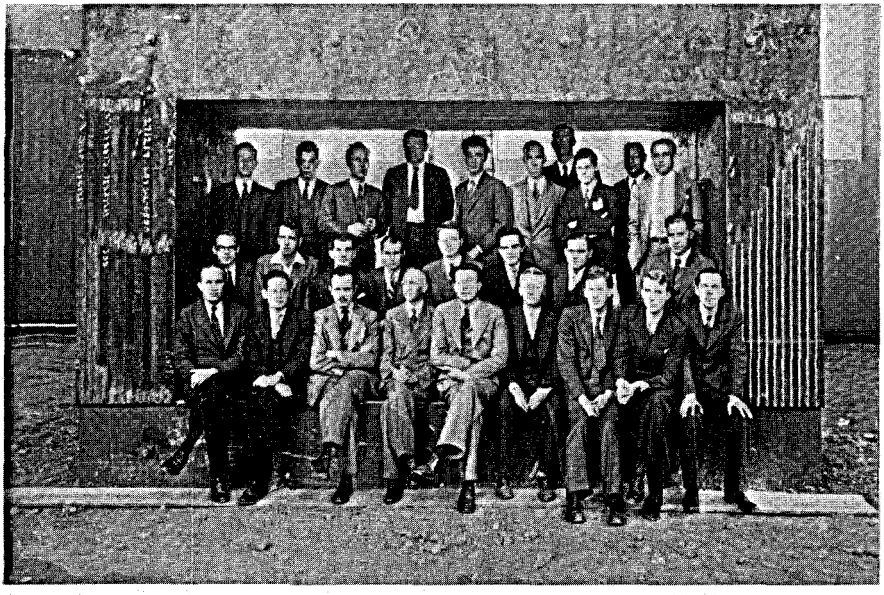
John H. Lawrence

Table of Contents

Beginning

The beginnings of what is now the Donner Laboratory and the Division of Biology and Medicine of the Lawrence Radiation Laboratory were firmly established in 1937 by the appointment of Dr. John H. Lawrence to the regular staff of the Radiation Laboratory and the faculty of University of California Medical School. The Radiation Laboratory was an entity under E.O. Lawrence in 1936.

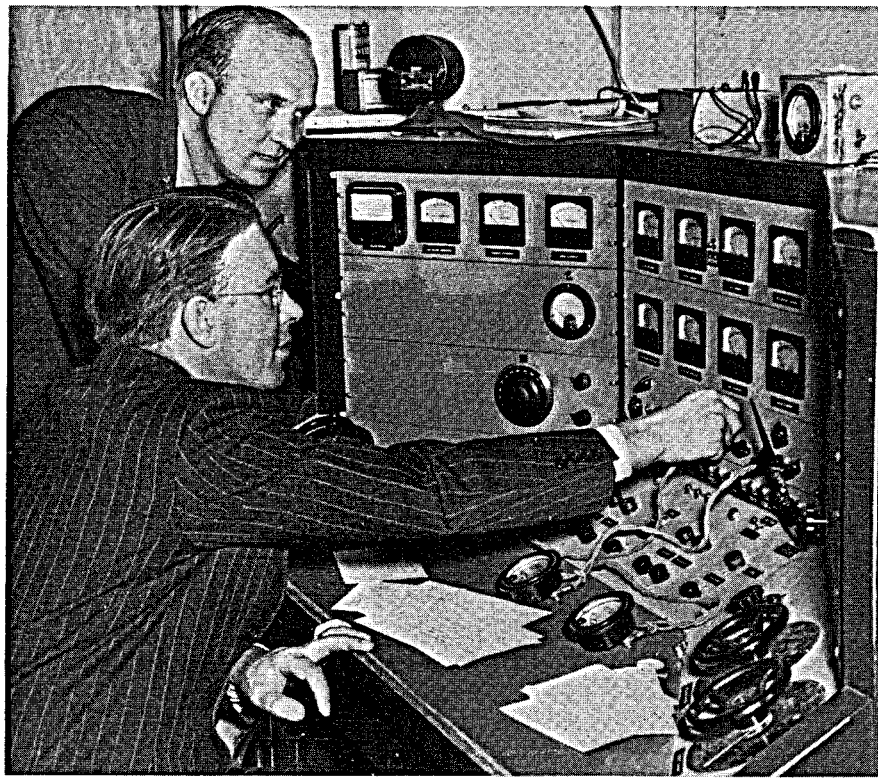
Prior to that time John Lawrence was at Berkeley on leave of absence from Yale University where, since 1934, he had been on the Yale Medical School faculty, but had begun collaborative work with his brother Ernest O. Lawrence and Paul A. Aebersold with work on the use of neutrons in the treatment of cancer which Dr. John Lawrence presented in 1936 before the American Society of Clinical Investigations. In 1936 and 1937 members of the Radiation Laboratory regular staff and visiting fellows are shown below.



(Left to right and top to bottom): A.S. Langsdorf, S.J. Simmons, J.G. Hamilton, D.H. Sloan, J.R. Oppenheimer, W.M. Brobeck, R. Cornog, R.R. Wilson, E. Viez, J.J. Livingood, J. Backus, W.B. Mann, P.C. Aebersold, E.M. McMillan, E.M. Lyman, M.D. Kamen, D.C. Kalbfell, W.W. Salisbury, J.H. Lawrence, R. Serber, F.N.D. Kurie, R.T. Birge, E.O. Lawrence, D. Cooksey, A.H. Snell, L.W. Alvarez, P.H. Abelson.

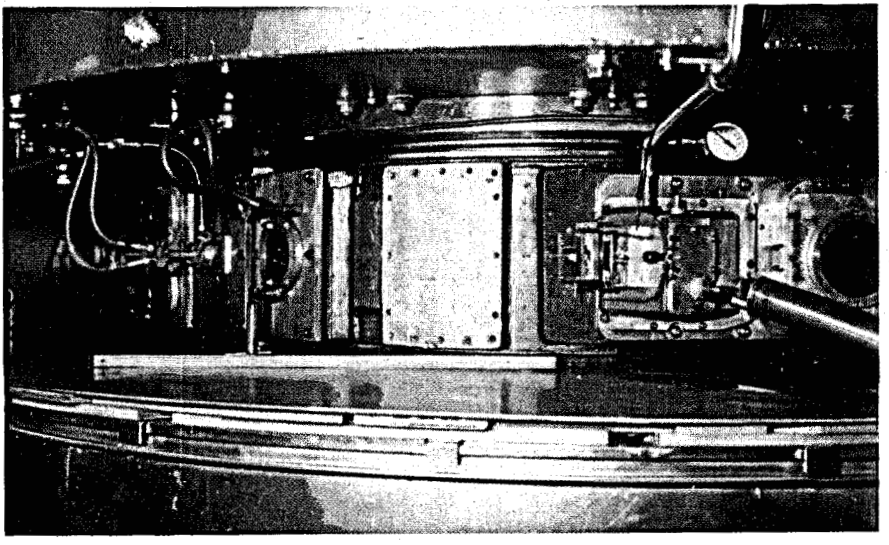
With the completion of the Crocker cyclotron in 1936, research in biology and medicine had a strong emphasis along with chemistry and physics at the Radiation Laboratory directed by E.O. Lawrence. During the first twenty years the major categories of truly pioneering work included exploration of the use of neutrons for therapy, establishment of radiation safety criteria, use of radioactive tracers for studies of human physiology and the treatment of disease, use of accelerated charged particle beams for therapy, development of radionuclide imaging instrumentation, establishment of the importance of cholesterol and lipoprotein abnormalities in heart disease, and exploration of the characteristics of yeast as a model for elucidation of genetic mechanisms.

The early history is documented by the selected publications whose titles describe the work accomplished to 1960.

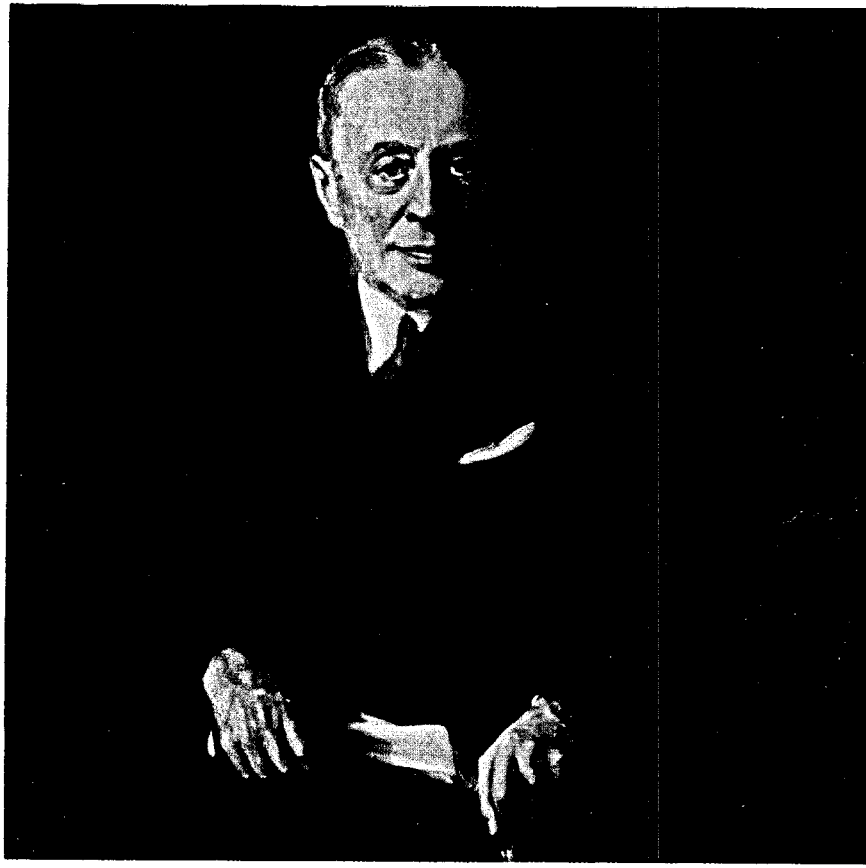


Drs. Ernest and John Lawrence at the controls of the 60-Inch Cyclotron.

Above is the Crocker Laboratory, which housed the Radiation Laboratory before the facilities at the Donner Laboratory and the Lawrence Berkeley Laboratory were built. *Below* is the beam from the 60-Inch Crocker Cyclotron.



THE DONNER LABORATORY
A GIFT OF
THE DONNER FOUNDATION
MARCH 14, 1941
IN MEMORY OF
JOSEPH WILLIAM DONNER
FOR THE APPLICATION OF PHYSICS,
CHEMISTRY, AND THE NATURAL SCIENCES
TO BIOLOGY AND MEDICINE



Donner Laboratory and Pavilion on the Berkeley Campus

In 1941, Donner Laboratory was built at the cost of $650,000 with financing of $465,000 from the International Cancer Research Foundation. This new home for biologists and physicians was named in honor of William H. Donner, who was the president of the International Cancer Research Foundation, which later was renamed the Donner Foundation. In fact the Donner Foundation had funds contributed entirely, or almost so, by Donner himself. Circumstances surrounding this donation were as follows. William H. Donner's son, Robert, had died of cancer, and as a result, his father was particularly interested in medical work on cancer. He heard about the treatment of cancer by neutron beams by Dr. John Lawrence and in 1940 Mr. Donner visited Dr. Ernest Lawrence and was greatly impressed with the work in progress. Near the end of his visit, Lawrence received $150,000 from Donner for a building to use for the work in Medical Physics. The actual construction of Donner Laboratory was started on July 21, 1941.

In the course of the decade after the establishment of Medical Physics, the increase in research work on human beings at Berkeley resulted in the establishment in 1954 of a special ward called The Donner Pavilion as an addition to Cowell Hospital to care for such patients. This was a two-story addition to the east wing of Cowell Hospital, finished in 1954 at a cost of $191,000, once again a gift from the Donner Foundation. The purpose of the Pavilion was "for research in radiobiology under supervision of the Donner Laboratory."

Academic Unit—Division of Medical Physics

The actual beginning of Medical Physics at the Radiation Laboratory evolved in two stages. In August of 1944, initial approval was given to appoint four faculty members, Drs. John Lawrence, Joseph Hamilton, Cornelius Tobias and Hardin Jones, to the newly created Division of Medical Physics, within the administrative framework of the UC Berkeley Physics Department. The official approval was granted by the Regents effective July 1, 1945 with specific recommendations as follows:

> "(a) There should be a nucleus of men including Drs. John Lawrence, Joseph Hamilton, Aebersold and Tobias who would hold joint appointments in the Medical School and in the Department of Physics, and then a second group of people who would play important parts in the development of medical physics, such as Doctors Miller, Chaikoff, Hamilton, Anderson, Robert Aird, Strait,

Low-Beer, Althausen, David Greenberg, C.L.A. Schmitt and Soley. This second group would be carrying out experimental studies and therapeutic studies through the Medical School."

There were additional written expectations and guidelines for the Division of Medical Physics. Of great importance was the proposal by Dr. John Lawrence that a small clinic in Berkeley could be considered a medical physics branch of the outpatient department of the hospital but

> "there should be no limitation or 'ham-stringing' of the freedom of the members of the subdivision of Medical Physics or others in the medical school to carry on treatment or investigations at Berkeley if research were the prime interest."

The Directors of Donner Laboratory in succession are: Dr. John Lawrence, Dr. James Born, Dr. Edward Alpen and Dr. Paul Silverman.

Department of Biophysics and Medical Physics

The Division of Medical Physics, though officially under the administrative aegis of the Department of Physics, operated as a self-administered group. Over a period of 42 years, academic programs became closely integrated with undergraduate and graduate units of the Berkeley campus under the leadership of Drs. Lawrence, Tobias and Jones. In 1979, that Division became the Department of Biophysics and Medical Physics at U.C. Berkeley and along with the Biophysics Group is responsible for 105 undergraduate students and approximately 100 graduate students.

Achievements and examples of ongoing activities to 1987 are illustrated throughout the remainder of this booklet.

ISOTOPIC TRACERS AND NUCLEAR RADIATIONS

With Applications to Biology and Medicine

by William E. Siri

with contributions by

Ellsworth C. Dougherty
Cornelius A. Tobias Rayburn W. Dunn
James S. Robertson Patricia P. Weymouth

Division of Medical Physics, Department of Physics, and Radiation Laboratory, University of California

FIRST EDITION

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NEW YORK TORONTO LONDON 1949

Historical Publications

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Hamilton, J.G.
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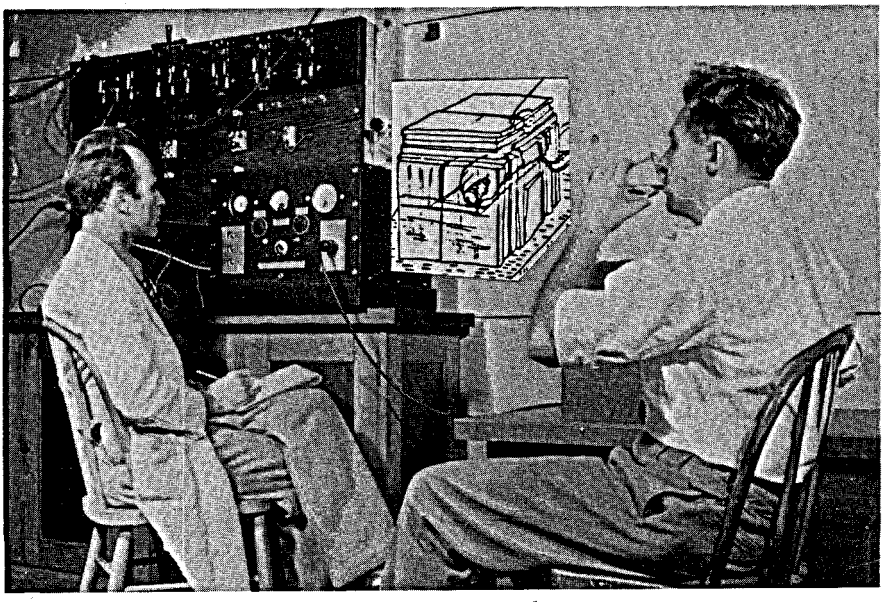
Joseph G. Hamilton



First medical physiology studies of the dynamics of sodium transport in the body by Dr. Hamilton involved observing the arrival of ^{24}Na in the hand vascular system after oral ingestion.

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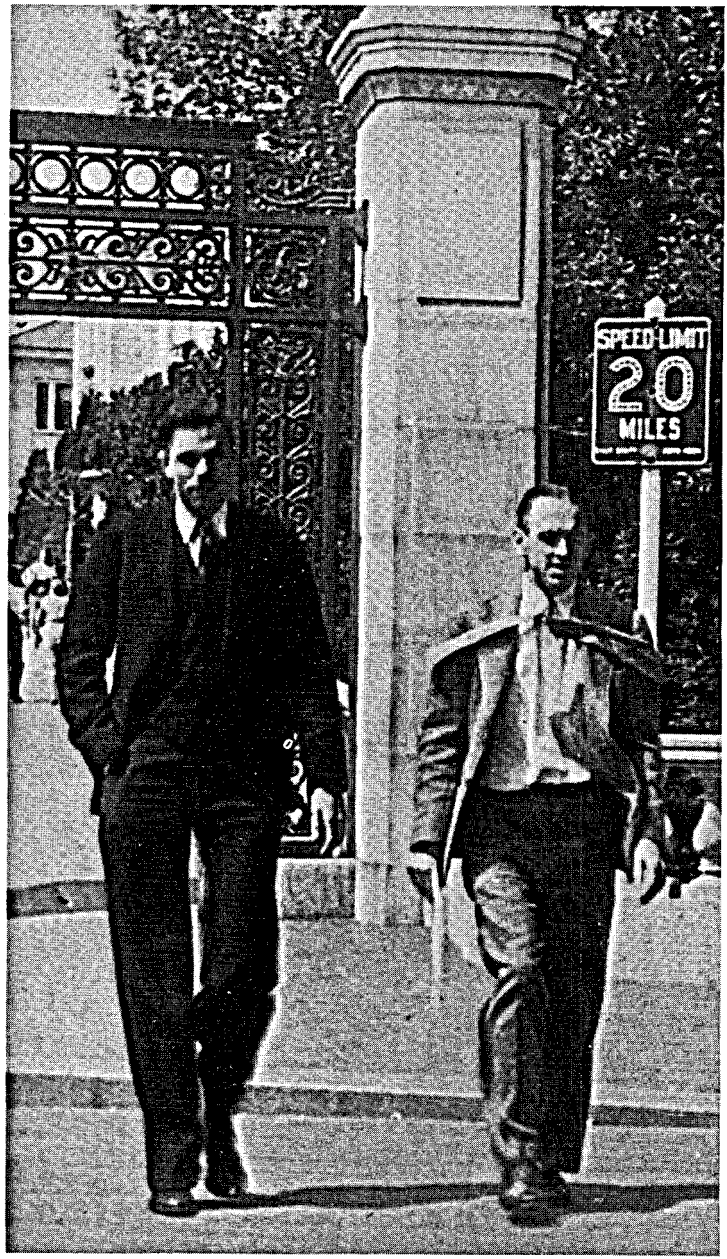


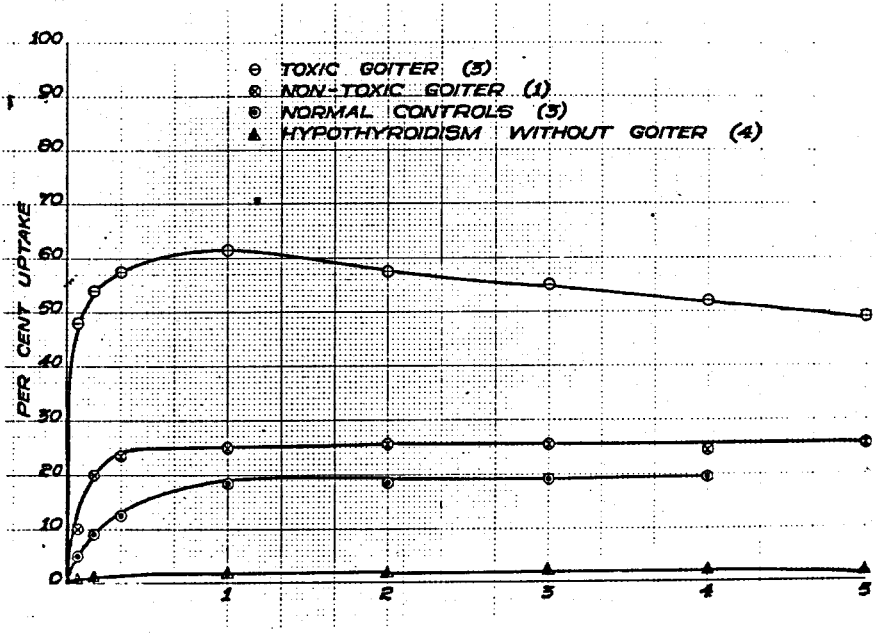
Drs. Glenn Seaborg and Jack Livingood at the U.C. Berkeley Campus Sather Gate in 1938, on their way to the branch post office to mail their manuscript on iodine-131, "Radioactive Isotopes of Iodine," to Physical Review.

^{131}I Discovery

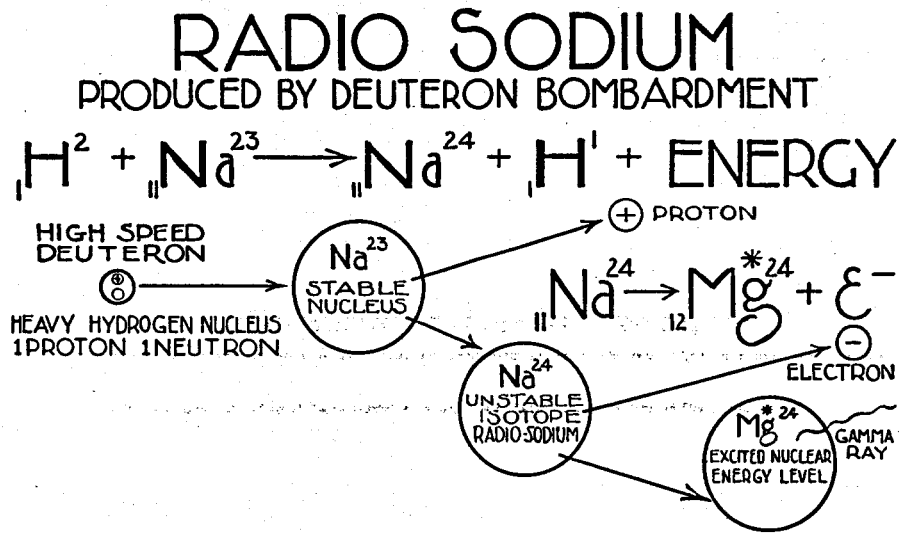
In the spring of 1938, Dr. Hamilton asked Dr. Seaborg if he could find an isotope of iodine with a half-life of "about one week." Dr. Jack Livingood prepared tellurium targets which were bombarded by deuterons and neutrons at the 37-Inch Cyclotron. After chemical separation, Drs. Seaborg and Livingood discovered ^{131}I (8-day half-life).

Right: The first kinetic study on the function of the human thyroid using ^{131}I and a Geiger-Muller counter.

Below: Disease diagnosis is made possible by patterns of the time variation of activity in the thyroid. The first studies were done by the Berkeley team in 1940.



Discovery of Radionuclides



β-PARTICLES EMITTED WITH AN AVERAGE ENERGY OF APPROXIMATELY.5MV
γ-RAY EMITTED WITH ENERGY OF 1MV, 2MV, 3MV, IN THE RATIO OF 3:3:2

E.O. Lawrence, Physical Review (1934)

Radionuclides used around the world in medicine discovered at LBL.

27/37-Inch Cyclotron		60-Inch	184-Inch
Oxygen-15	Gallium-67	Hydrogen-3	Magnesium-28
Fluorine-18	Rubidium-86	Carbon-14	Iron-52
Calcium-45	Molybdenum-99	Magnesium-28	Copper-67
Chromium-51	Technetium-99m	Potassium-43	Zinc-62
Manganese-52	Tin-113		Germanium-68
Manganese-54	Iodine-124	Iodine-123	
Iron-59	Iodine-130	Mercury-197	Rubidium-82
Cobalt-57	Iodine-131		Strontium-82
Cobalt-58	Iodine-132		Cesium-129
Cobalt-60	Xenon-133		Thallium-201

Discovery of Technetium-99m
(the most commonly used isotope in medicine)

Nuclear Isomerism in Element 43

We wish to report briefly an interesting case of isomerism which has appeared during an investigation of the short-lived radioactive isotopes of element 43. The irradiation of molybdenum with deuterons or slow neutrons produces a radioactive molybdenum isotope with a half-life of 65 hours which emits electrons with an upper energy limit of approximately 1 Mev. (This molybdenum activity has also been reported recently by Sagane, Kojima, Miyamoto and Ikawa.)[1] This molybdenum decays into a second activity which has a half-life of 6 hours and which emits only a line spectrum of electrons. Since the molybdenum emits electrons, the daughter activity must be ascribed to element 43; chemical identification has been carried out and has confirmed this identification of the 6-hour activity. Absorption measurements in aluminum and measurements with a magnetic spectrograph[2] indicate an energy for the electrons of about 110 kev. This line spectrum must be due to the conversion electrons of a gamma-ray of about 130 kev energy. The 6-hour activity also emits x-radiation and γ-radiation. The absorption of the x-rays in molybdenum, columbium and zirconium shows a discontinuity that is consistent with the $K\alpha$ line of element 43, which is to be expected on the basis of the interpretation given below.

The simplest and most reasonable explanation for these facts is the existence of an excited state in this isotope of element 43 which reverts to the ground state by the emission of conversion electrons and gamma-rays with a half-life of 6 hours. A line of conversion electrons corresponding to a similar transition seems to have been detected by Pontecorvo[3] during a study of the nuclear isomerism in rhodium. A more complete discussion and a description of the experiments will be published later in the *Physical Review*.

We wish to thank Professor E. O. Lawrence for the privilege of working with the cyclotron and for his interest in this problem.

We wish also to express our appreciation to Mr. D. C. Kalbfell for the photographing of the line spectrum of electrons. This research has been aided by grants from the Research Corporation.

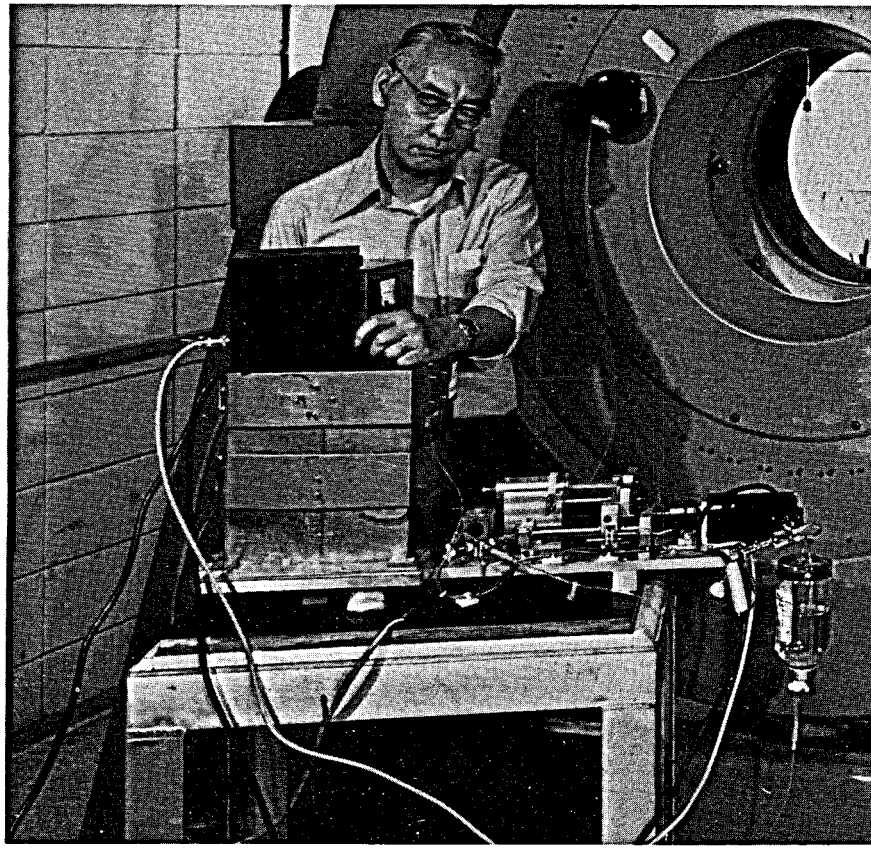
E. SEGRÈ
G. T. SEABORG

Radiation Laboratory,
Department of Physics (E.S.),
Department of Chemistry (G.T.S.),
University of California,
Berkeley, California,
October 14, 1938.

[1] Sagane, Kojima, Mijamoto and Ikawa, Phys. Rev. 54, 542 (1938).
[2] Kalbfell, Phys. Rev. 54, 543 (1938).
[3] Pontecorvo, Phys. Rev. 54, 542 (1938).

Physical Review 54, 772, 1938

Radionuclide Generators



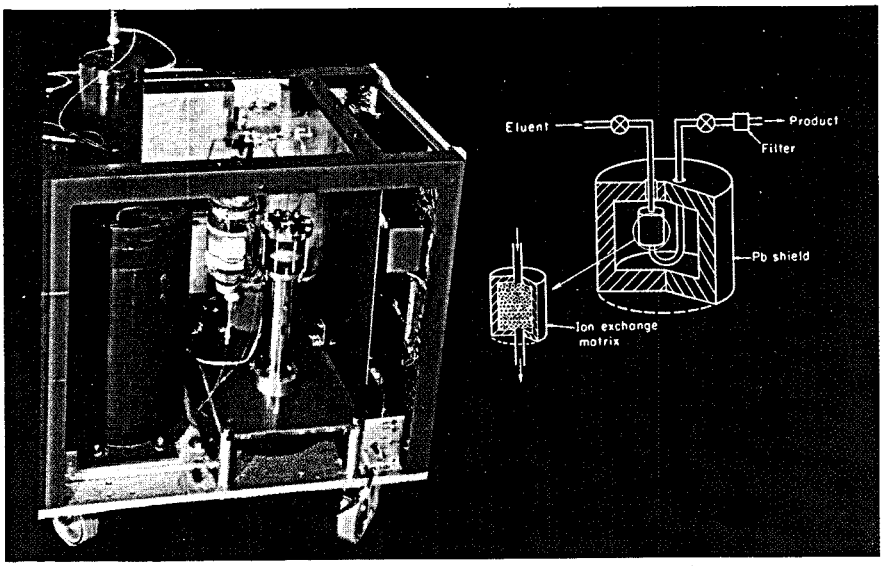
Generators for single photon imaging

Parent	Half-life	Daughter	Half-life	Gammas MeV (%)
Rb-81*	4.7 h	Kr-81 m	13.0 s	0.190(67)
Mo-99	2.8 d	Tc-99 m	6.0 h	0.140(90)
Sn-113	115.0 d	In-113 m	1.7 h	0.393(64)
W-178	21.5 d	Ta-178	9.4 m	0.129(25)
Os-191	15.0 d	Ir-191 m	4.9 s	0.129(25)
Hg-195 m	41.6 h	Au-195 m	30.5 s	0.262(68)

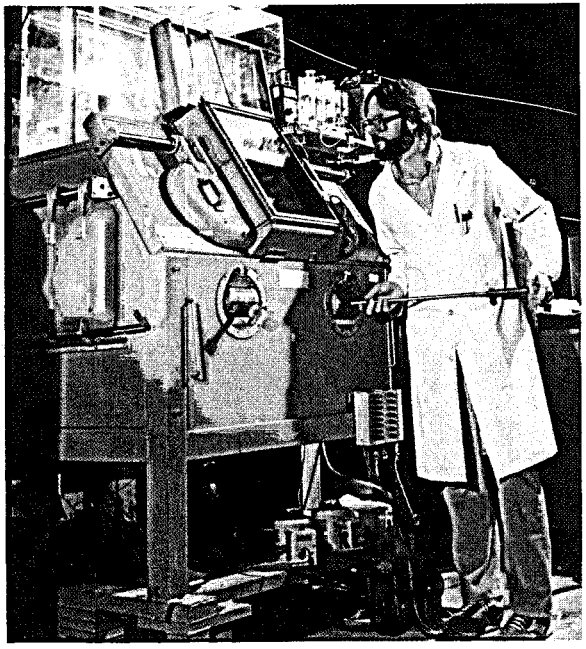
Generators for positron emitters

Parent	Half-life	Daughter	Half-life
Fe-52	8.3 h	Mn-52 m	21.1 m
Zn-62	9.1 h	Cu-62	9.8 m
Ge-68*	275.0 d	Ga-68	68.0 m
Sr-82*	25.0 d	Rb-82	75.0 s
Te-118	6.0 d	Sb-118	3.5 m
Xe-122*	20.1 h	I-122	3.5 m
Ba-128*	2.43 d	Cs-128	3.8 m

*Developed by Yukio Yano shown above with one of the ^{82}Rb portable systems.



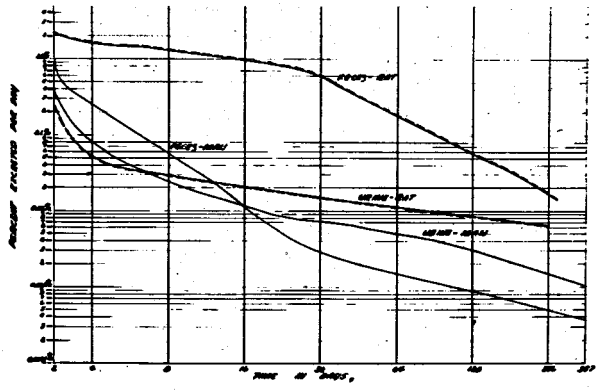
Strontium-82/Rubidium-82 generator first developed 20 years ago by Yukio Yano.



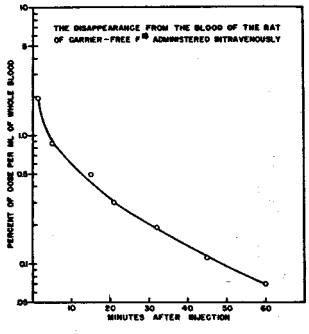
Xenon-122/Iodine-122 generator perfected for practical human use by Dr. Chet Mathis.

Radiation Hazards and Safety

The first studies on the biological distribution of isotopes discovered at Berkeley as well as other available radionuclides were conducted by Drs. Joseph Hamilton and Patricia Durbin. The radiation standards are based on their data. The joint involvement by these investigators in both the medical uses of tracers and their potential hazards resulted in a remarkable history on the safe use of a potentially dangerous new investigative tool. Drs. John Lawrence and Paul Aebersold took responsibility for studies of the hazards of neutrons in the mid-30s, and Drs. Cornelias Tobias, John Lawrence, Stanley Curtis and Eleanor Blakely have since investigated the hazards and benefits of charged particles.



Comparison of the excretion of plutonium in man and the rat following intravenous administration.



Earliest studies of the blood clearance of ^{18}F by Dr. Patricia Durbin.

Autoradiograph (right) studies of bone distribution of plutonium.

Treatment of Disease by Radioactive Isotopes

Phosphorus-32

The first use of a radioactive isotope for the treatment of disease was by Dr. John Lawrence on Christmas Eve 1936. This work came after extensive studies of the biological distribution of Phosphorus-32. The first patient had chronic leukemia and the Phosphorus-32 inhibited the abnormally high production of white cells by the bone marrow. This treatment was a successful precursor to therapy of some leukemias prior to the present distribution of chemotherapy and bone marrow transplantation.

The most remarkable early use of Phosphorus-32 in therapy was the treatment of polycythemia vera, a disease of an excessive number of red cells. The rationale was that the radioactive phosphorus would inhibit the progenitors of red cells. This form of treatment is still in use today. The treatment was so effective, in fact, that Dr. Lawrence was called upon to treat Cardinal Stepinac while under house arrest in Zagreb by Tito in 1953.

Iodine-131

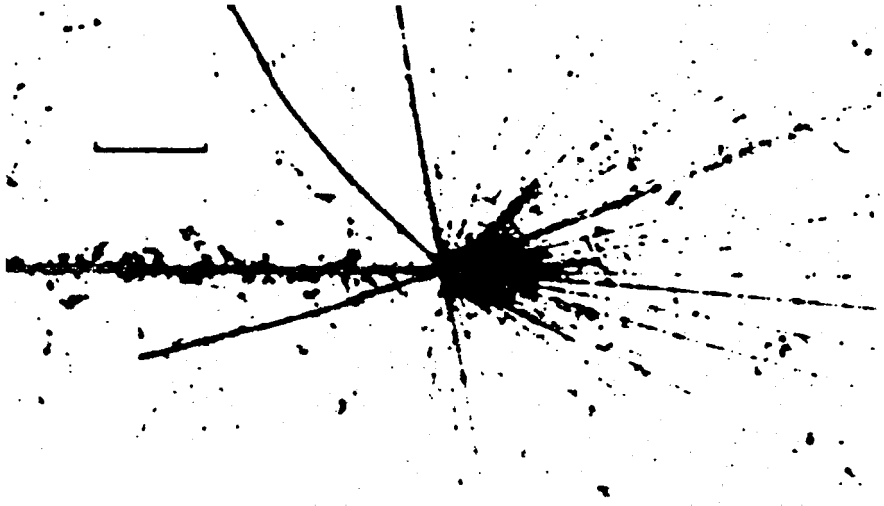
Drs. Joseph Hamilton and Mayo Soley of the UC San Francisco Medical School treated hyperthyroid patients with Iodine-131 discovered and produced at Berkeley.

Other Radionuclides

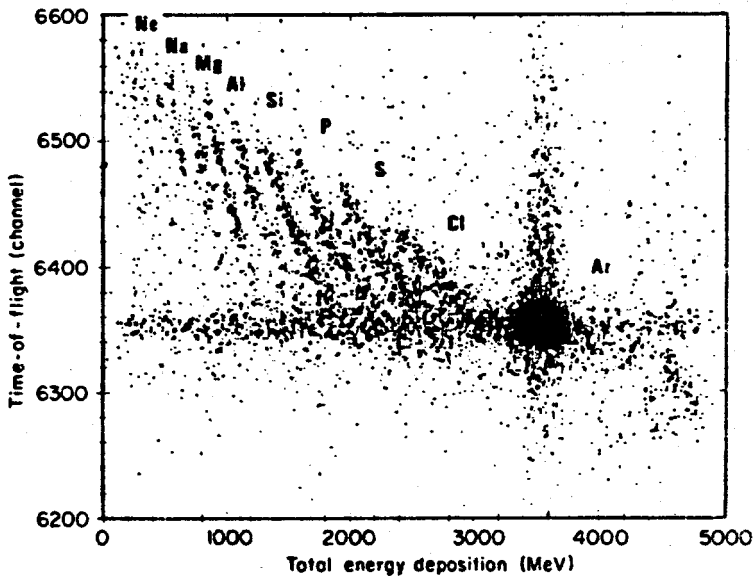
Yttrium-90 was used by Dr. Saul Winchel and William Loughman in attempts to treat leukemia. Yttrium-90 seeds were used for the treatment of pituitary disease, and Iodine-125 and Cobalt-60 are used for treatment of tumors by implantation of radioactive seeds.

The potential of charged particles for deposition of radiation energy in known regions of the body led to a major emphasis on the application of accelerators to the treatment of disease in the late 1950s with a shift in focus from the use of radionuclides for therapy to the use of radionuclides for diagnostic imaging studies by the Donner scientists.

Heavy Ion Interaction Physics

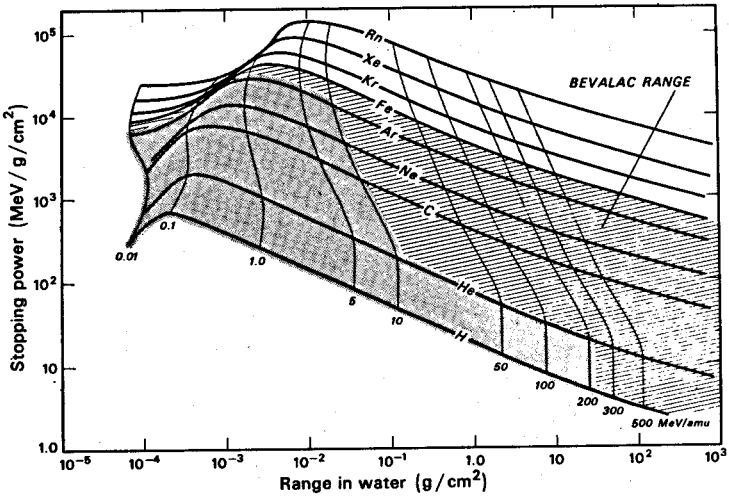


Accelerated charged particles scatter, fragment, and can disintegrate another nucleus as shown in the case above. The high energy release along and particularly at the end of the ion path causes radiation damage including DNA strand breaks.

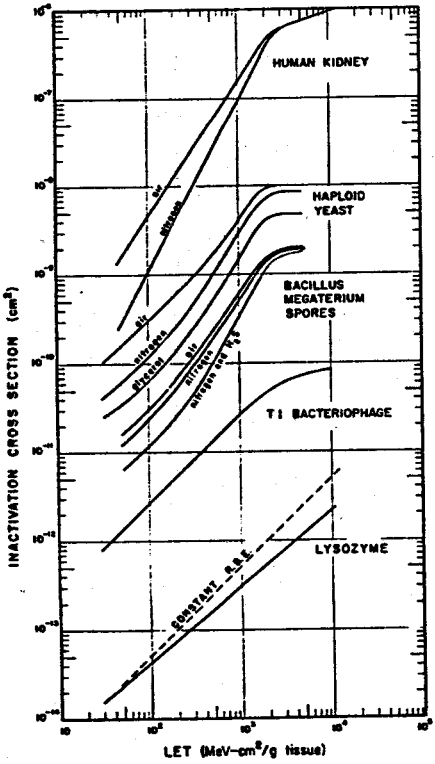


The variety of ion fragments and their velocities are analyzed by Dr. Schimmerling and coworkers.

Heavy Ion Radiation Advantages



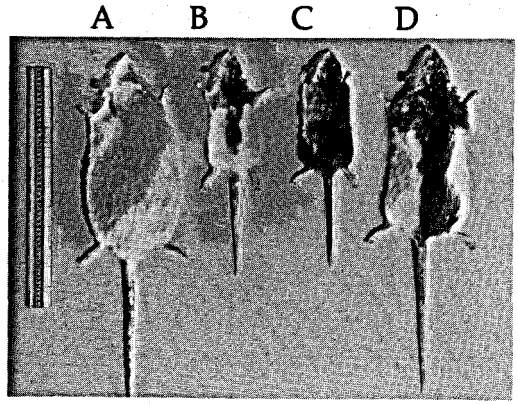
INACTIVATION CROSS SECTIONS



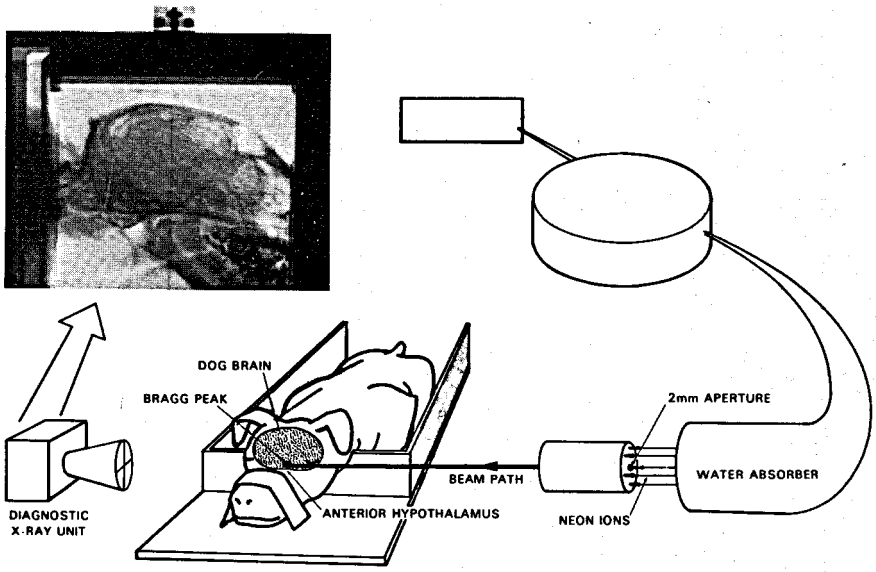
The physical advantages of charged particles are their potentials for focusing into the body for precise energy deposition and secondly the high transfer of ionization energy which increases with the atomic number of the nucleus and increases as the velocity of a given nucleus decreases. The effects of energy deposition on biological tissues are shown by Drs. Paul Todd and Cornelius Tobias. These studies are being continued by Drs. Eleanor Blakely, Tracy Yang, Ruth Roots, John Ainsworth, Edward Alpen, Stanley Curtis, and others.

Medical Use of Accelerated Charged Particles

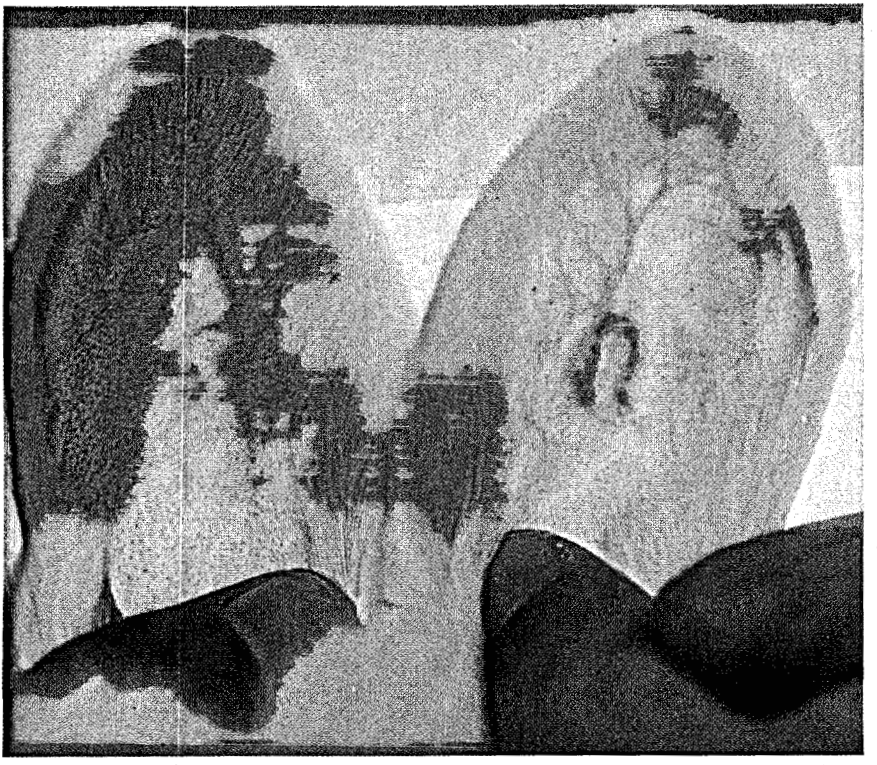
First proof of the efficacy of accelerated protrons for ablation of the pituitary was in 1948 by Dr. Cornelius Tobias and other Donner scientists.

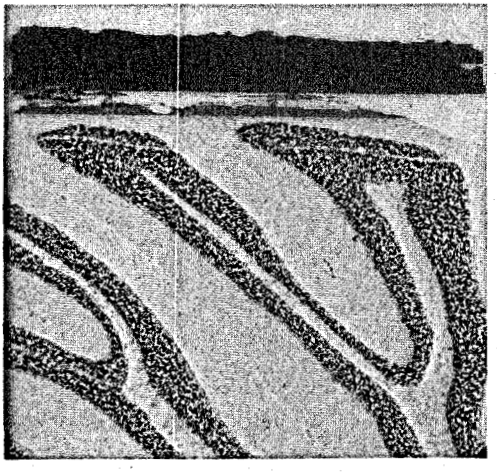


A and D are control, well-fed rodents. B is a surgically hypophysectomized rat, and C is a rat 5 months after pituitary irradiation with a narrow beam of deuterons, 1954.



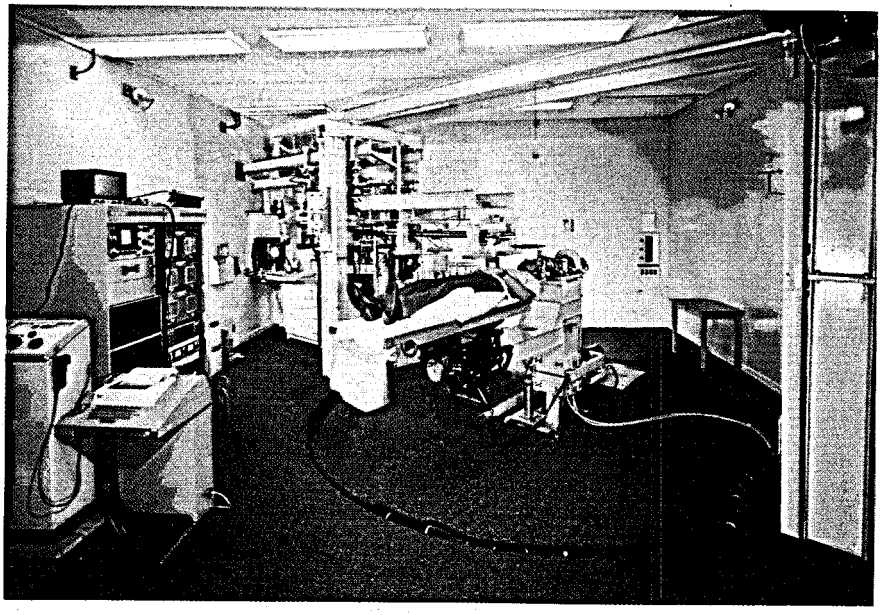
Studies of the function of the anterior hypothalamus and the reponse of the CNS to charged particles by Drs. Kathleen Brennan, Kenneth Frankel, Peter Valk, and others.



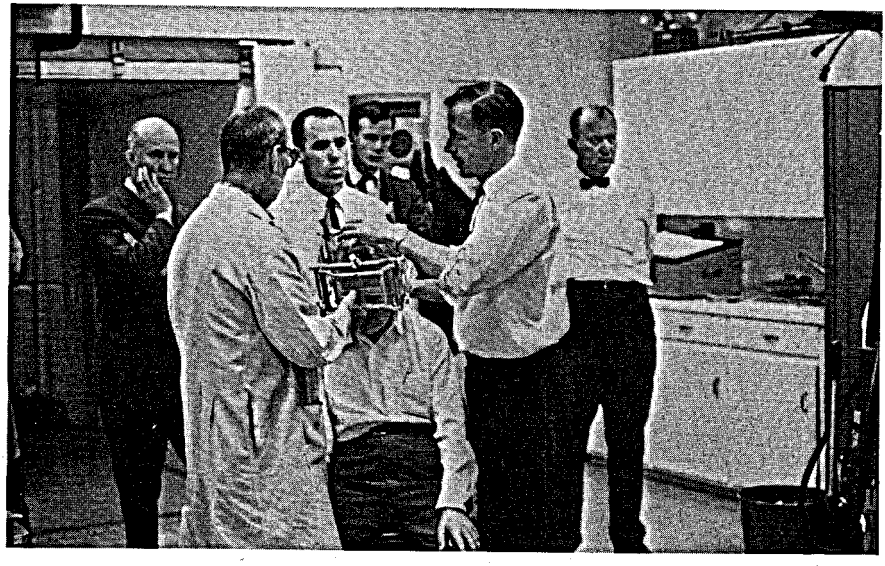


Laminar Lesion

Upper: Charged particle stopping beam effects on living tissues is studied to determine safe doses for treatment of cancer. *Lower:* Thin Bragg peak of protons in early experiments by Drs. Cornelius Tobias, Donald Van Dyke, and John Lawrence.



John Lyman in his Irradiation Stereotactic Apparatus, Human (ISAH). Subsequent patient and treatment planning methods were developed by Drs. George Chen, William Chu, Sam Pitluck, Todd Richards, Sheri Henderson, Paula Petti, Michael Collier and Marc Kessler.



First Parkinson's patient treated (1965).

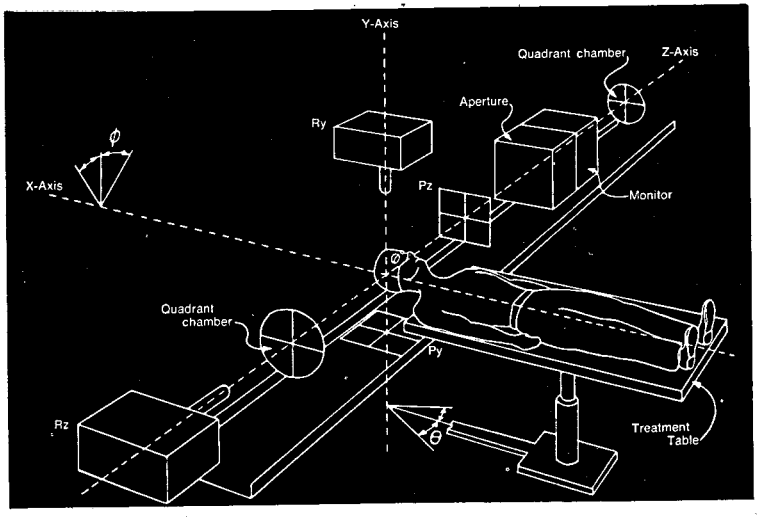
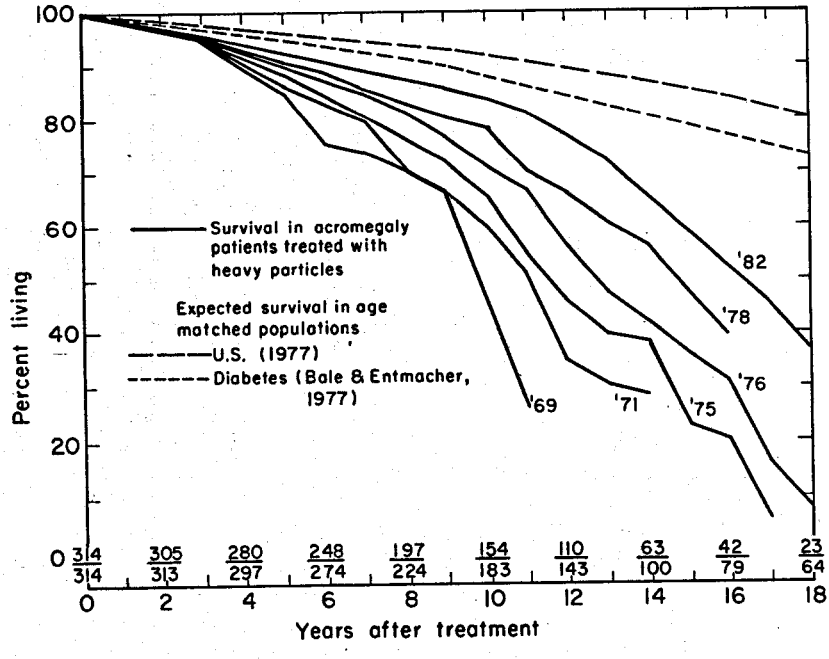
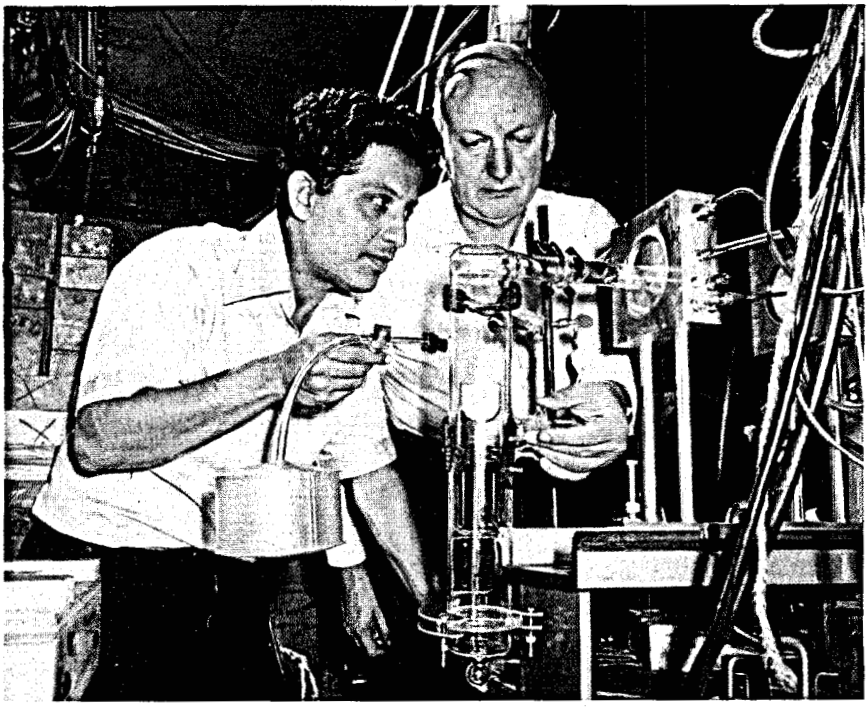
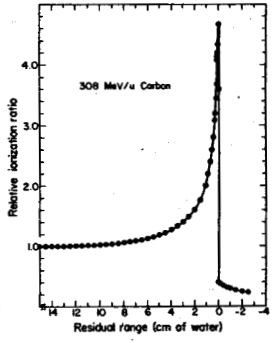


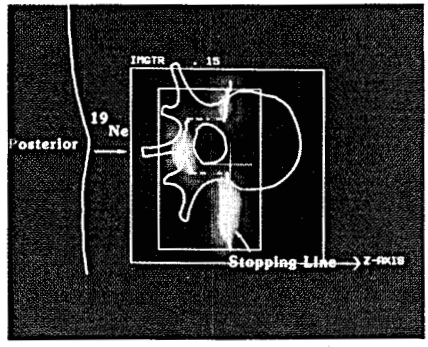
Diagram of the stereotactic setup for administration of heavy-particle irradiation to the sella turcica.



Survival data for patients treated for acromegaly. Since the majority of the patients are alive, the curves will continue to approach the survival curves of age and sex-matched general population.

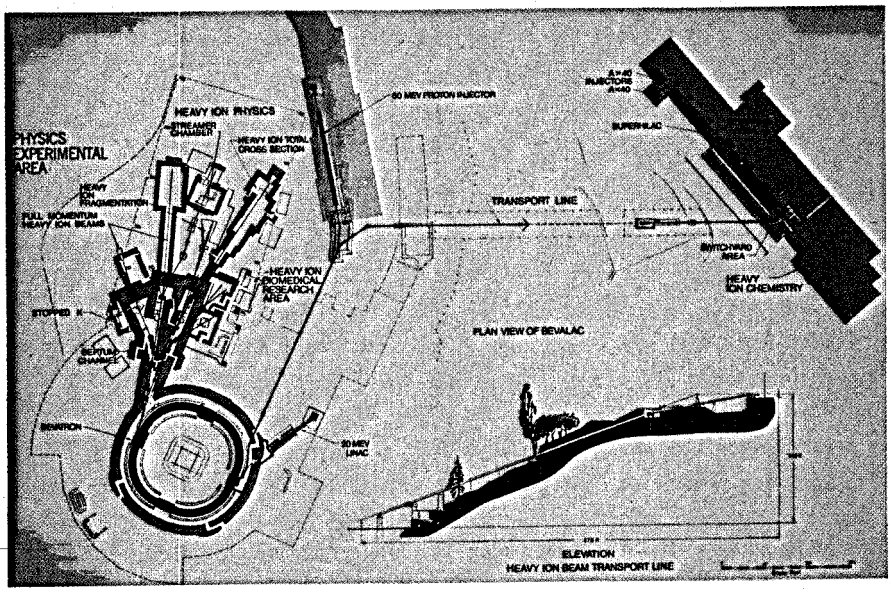




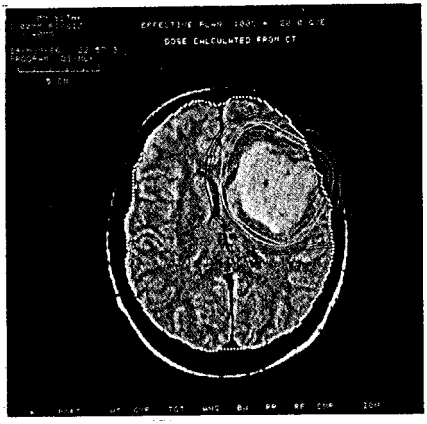


Positron emitting isotopes (^{15}O, ^{10}C, ^{11}C, ^{13}N, ^{19}Ne) can be produced by the spallation of accelerated nuclei in tissues or by actually accelerating beams of the short half-life positron emitters to specific energies. These beams will stop in a small volume of tissue at a depth which depends on the energy. Photons are released when the positron encounters an electron which is usually at the Bragg peak position. These annihilation photons are used to spatially locate the position of the beam using positron tomography. *Top:* Drs. Chatterjee and Tobias are developing the method of implanting positron emitters as tracers for physiological studies. *Left:* Bragg curve of carbon for a depth from the surface of tissue of 14 cm. *Right:* Image of the treatment plan for neon where the stopping beam is adjusted in range to avoid the spinal cord.

Bevatron Joins the Hilac to Bevalac



At the suggestion of Al Ghiorso the HILAC was joined to the Bevatron for accelerating heavy ions in the mid-1970s.

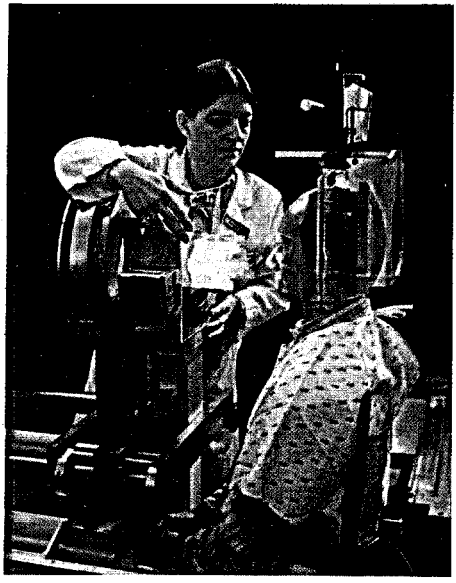


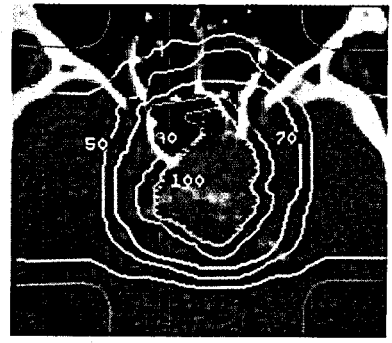
Brain tumor revealed using NMR is treated by Dr. Joseph Castro's stopping neon beams. The contours reflect the dose distribution.

Medical trials show the improvement in local control in neon ion treatment over conventional photon treatment. (Data from LBL and UCSF)

Tumor Site	Neon Ions	Photons
Glioblastoma Brain	17 mo.* 13 pts	9–12 mo.*
Nasopharynx Paranasal sinus	63% 21 pts	21%
Salivary gland	80% 10 pts	28%
Lung	39% 18 pts	22–40%
Prostate	100% 9 pts	≈60–70%
Sarcoma	45% 24 pts	28%

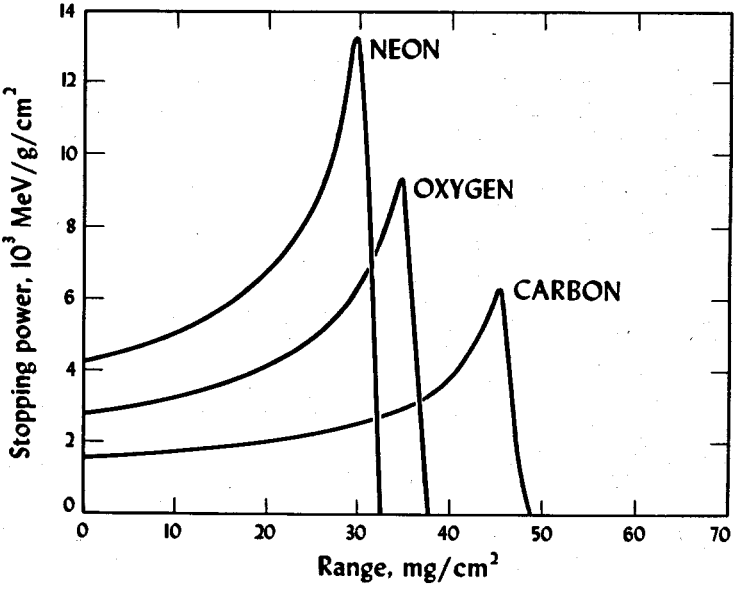
*median survival





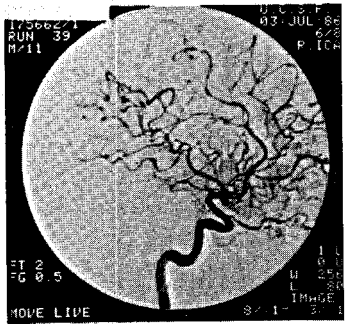
Contours on an X-ray tomograph show the radiation treatment plan.

Bevalac provides charged particles such as neon, which is being used to treat a patient with clivus cordoma.

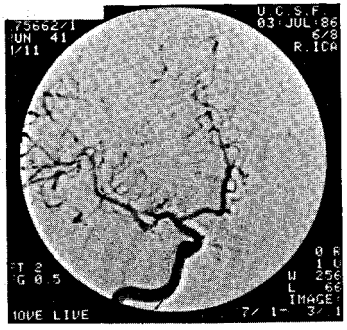


The ratio of energy between the stopping point and the entry point is greater for the greater Z of the ion. Also, the capability to focus into tumors is better with carbon and heavier ions than with protons and helium ions.

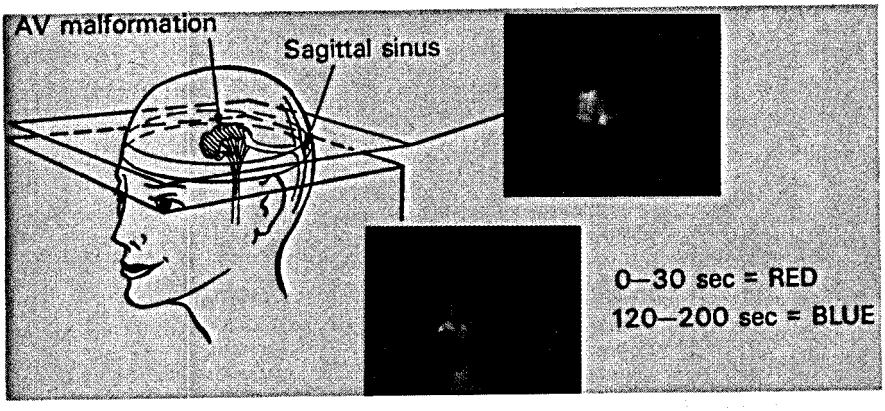
Treatment of Arteriovenous Malformation by Charged Particles



Before



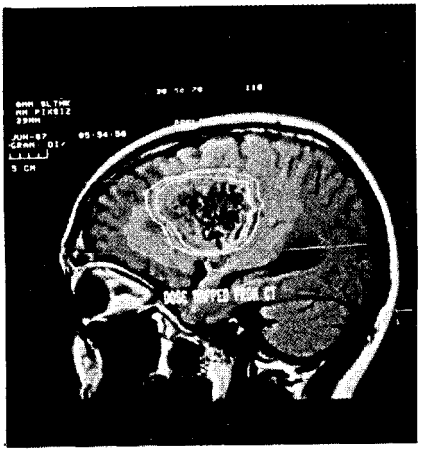
After



Above is shown the arterial-venous network in a patient before and after treatment by helium ions by Dr. Jacob Fabrikant. Small lesions deep in the brain and large malformations, which are difficult to treat by neurosurgery, have been treated successfully by charged particles.

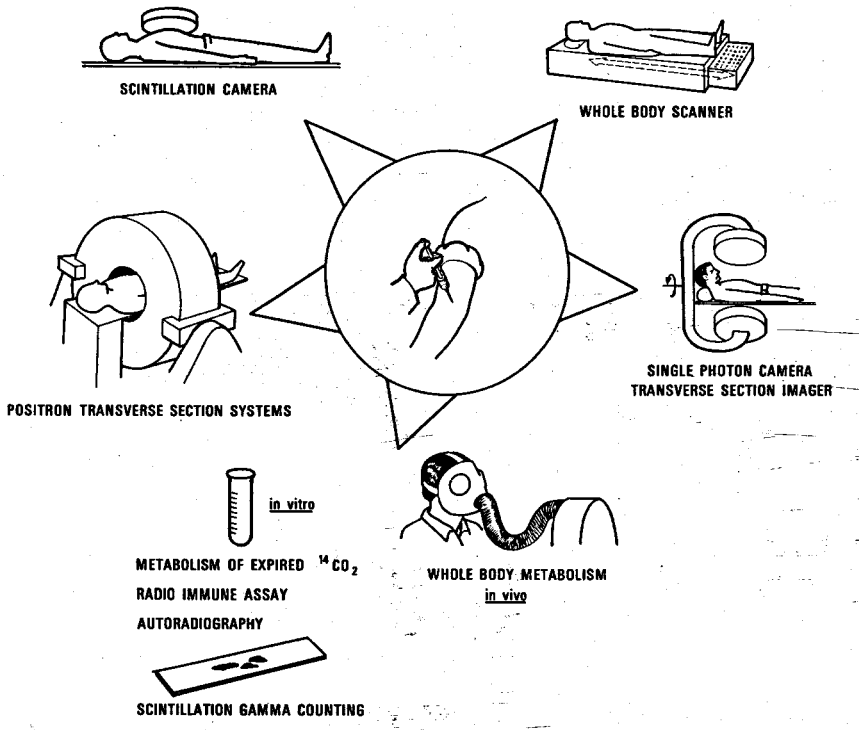
Middle images show blood volume by PET.

Right is the treatment plan (contours) of a large A-V malformation.



Radioactive Tracer Studies

Fundamental aspects of plant, animal, and human physiology were studied with the newly discovered radionuclides. The availability of these tracers and the quest for knowledge in human biology motivated the development of nuclear instrumentation shown below.



First Carbon-11 Studies of Plants

S. Ruben, Hassid WZ and Kamen MD: Radioactive Carbon in the Study of Photosynthesis. *J. Am. Chem. Soc.*, March, **1939.**

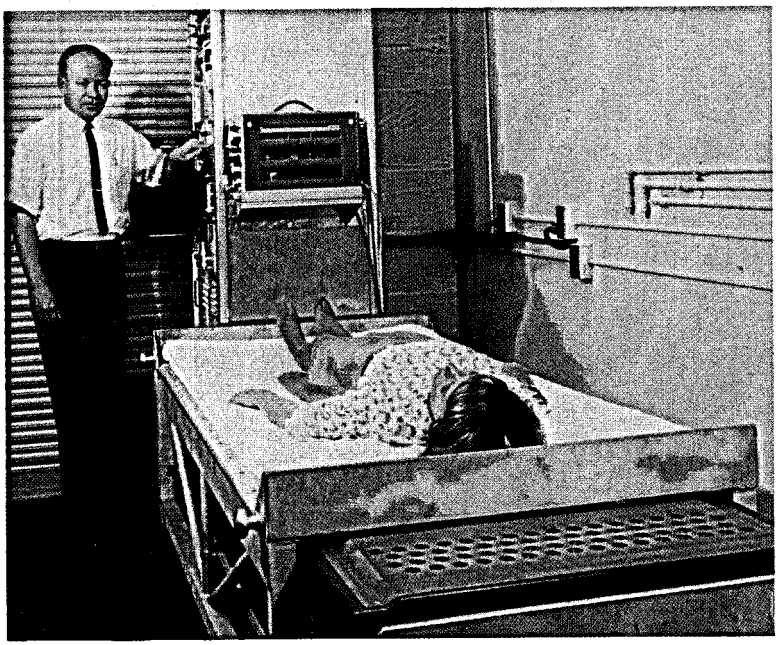
First Nitrogen-13 Studies of Plants

S. Ruben, Hassid WZ and Kamen MD: Radioactive Nitrogen in the Study of N_2 Fixation by Non-Leguminous Plants. *Science*, June, **1940.**

First Carbon-11 Studies in Human Subjects

C.A. Tobias, Lawrence JH, Roughton FHW, Root WS, Gregersen MI: Elimination of Carbon Monoxide from the Human Body with Reference to the Possible Conversion of CO to CO_2. *Am. J. Physiol.*, **1945.**

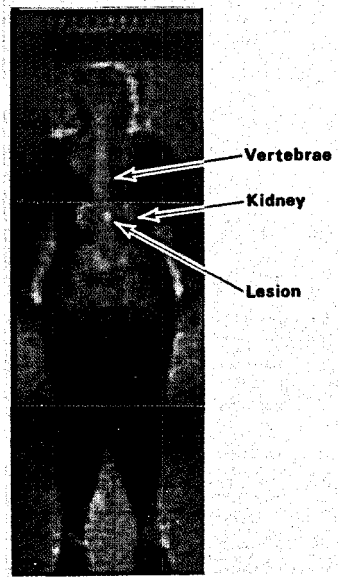
Whole Body Scanner



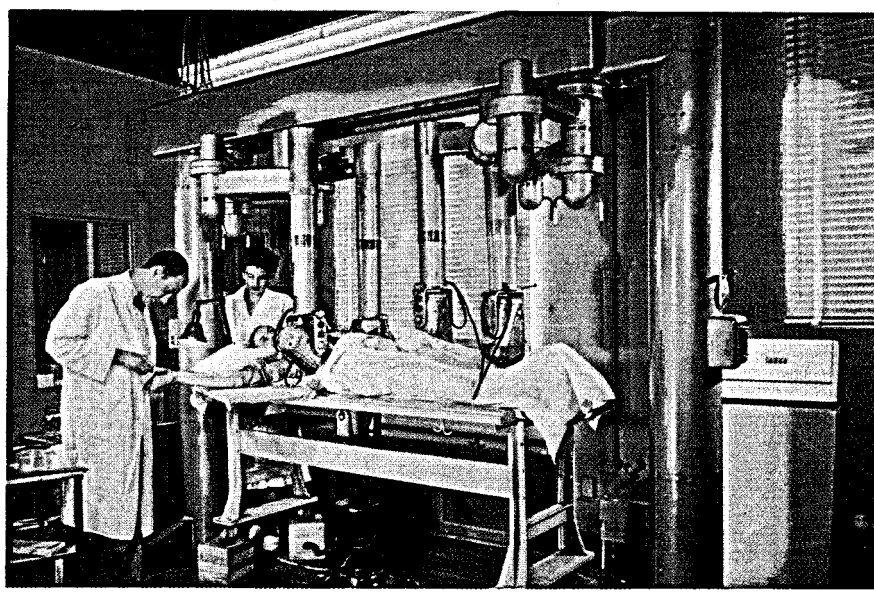
H.O. Anger's whole-body scanner was designed to image the spatial distribution of radionuclides such as Fe-59, I-131, and Tc-99m.

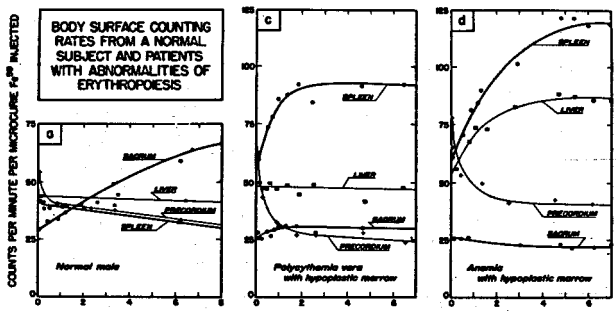
Right: This marvelous system was interfaced to a digital system by Dr. Budinger 17 years ago, and the first studies of bone Tc-99m pyrophosphate were performed by Y. Yano, Dr. Donald Van Dyke, and Dr. James McRae.

WHOLE BODY SCAN (64 x 384)
^{99m}Tc-EHDP



Hematology with Tracers

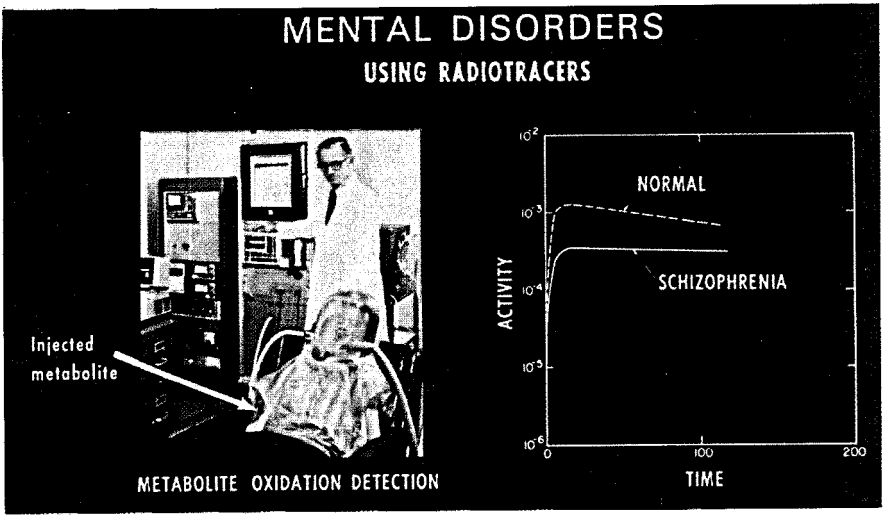




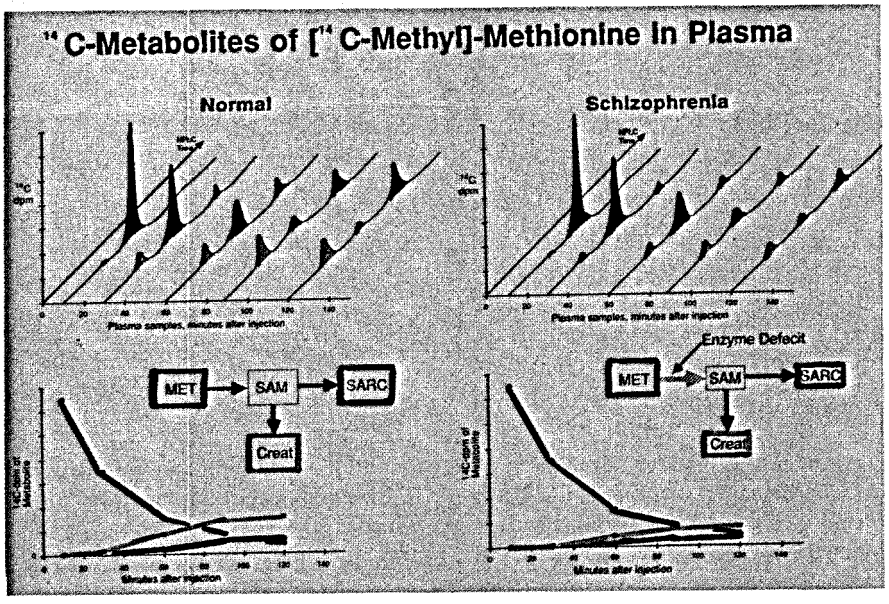
The movement of radioactive tracers through the body was an early application of the Multiprobe Detector "Monster" for in vivo kinetic analysis. Iron-59 was used in pioneering studies by Drs. Rex Huff, T. Hennessy, Myron Pollycove, Saul Winchell, and others.

Hematopoiesis

From the use of ^{59}Fe for the study of bone marrow production and ^{32}P for the treatment of polycythemia by Drs. Lawrence, Louis Wasserman and others, evolved intense studies for the cell biology of blood cell formation by Drs. Shirley Ebbe, Jack Schooley, Gisela Clemons, and George Brecher. An essential finding of these studies is the importance of the matrix environment.



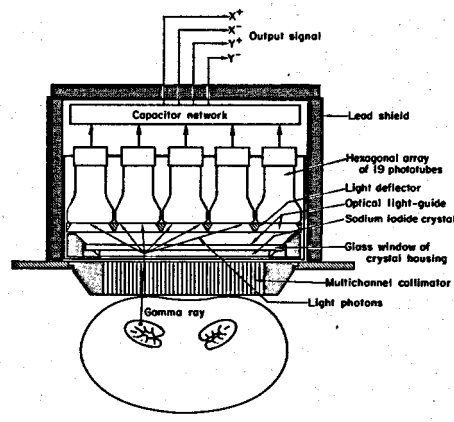
Abnormal methionine oxidation was observed in patients with schizophrenia in 1967 by Drs. Thornton Sargent and David Israelstam.

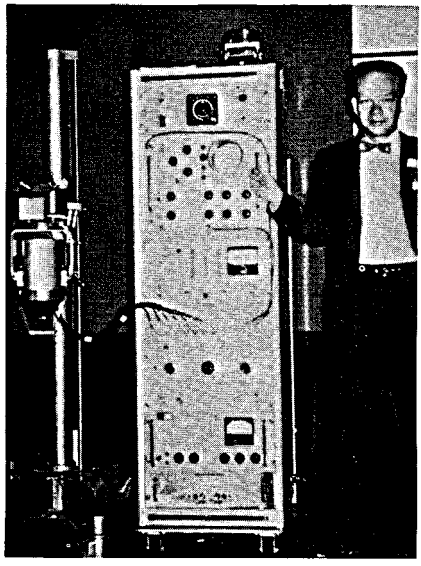


Hypothesis being tested is that an enzyme defect leads to abnormal methylation.

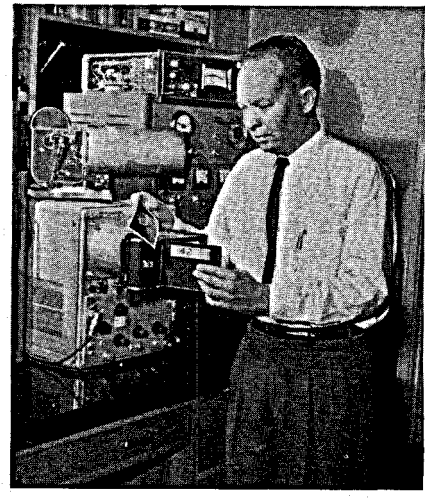
The Anger Camera

Photons from radionuclides interact in a NaI(Tl) crystal, and the light scintillations are detected by photoelectron multiplier tubes. The position of the light flash (scintillation) is computed electronically.

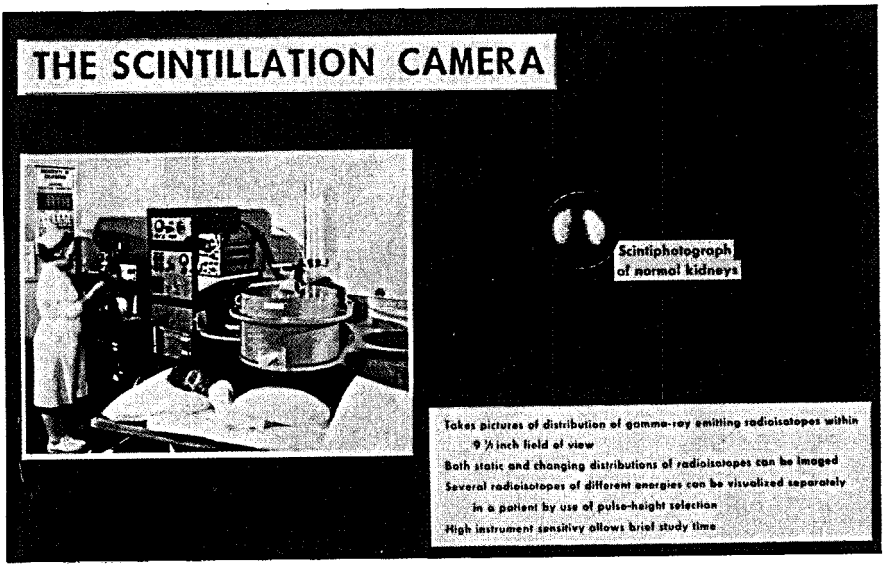


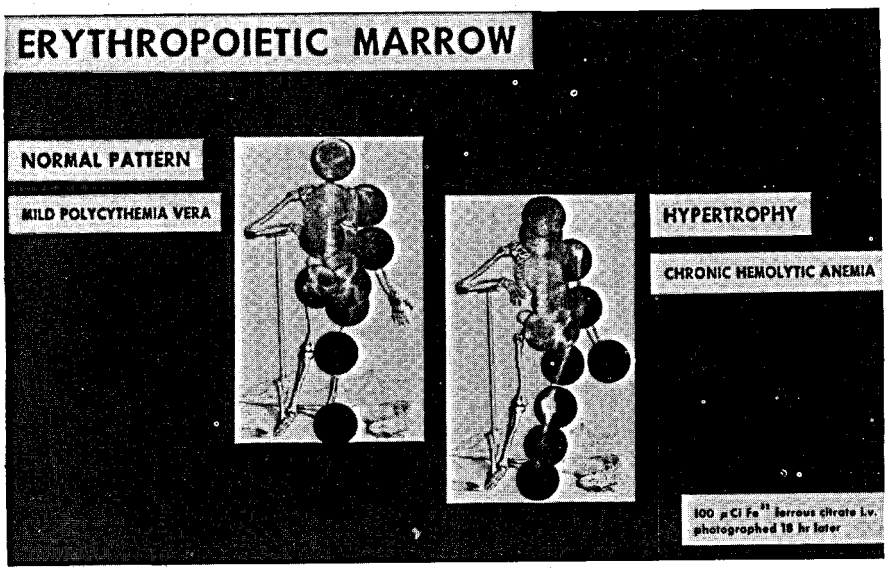


Hal Anger and his first scintillation camera displayed in 1954 at the 5th Meeting of the Society of Nuclear Medicine.



Scintillation positions were transferred to a cathode ray tube screen from which data were recorded on photographic film.

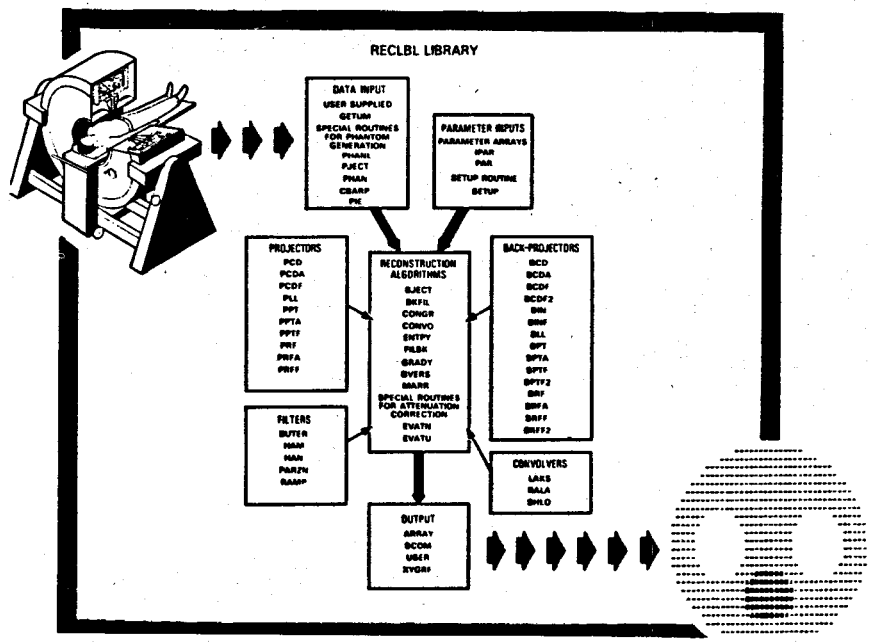




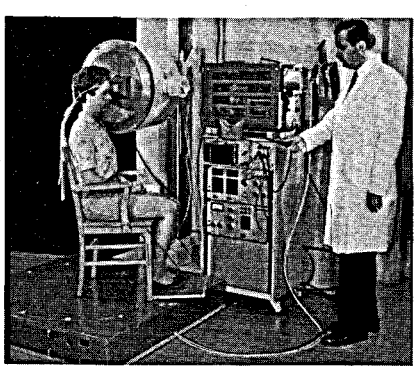
Using the positron emitter Fe-52 and the first positron camera the patterns of bone marrow activity in hematological disorders are revealed by Dr. Donald Van Dyke and Hal Anger.

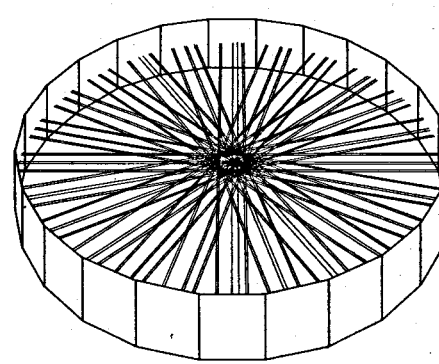
DONNER ALGORITHMS FOR RECONSTRUCTION TOMOGRAPHY

R.H. Huesman, G.T. Gullberg, W.L. Greenberg, T.F. Budinger

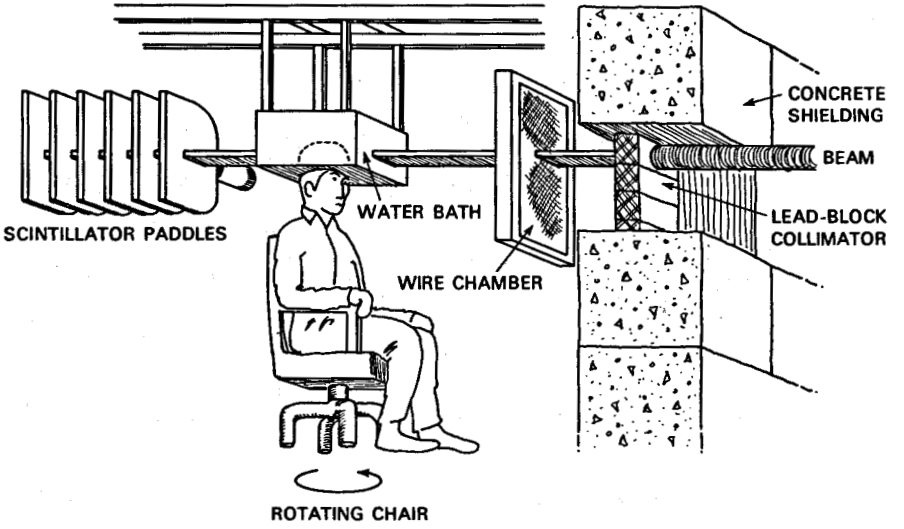


Three-dimensional reconstruction of radionuclide distributions was done in the late 1960s at Donner Laboratory by analogue back projection methods (below) with the Anger camera by Drs. David Price, Hirsh Hanmaker, James McRae and Hal Anger (Dr. Kuhl's work was 1963). In 1973 the Donner team (above) did the first quantitative digital reconstructions and created the computer library of methods in use throughout the world.



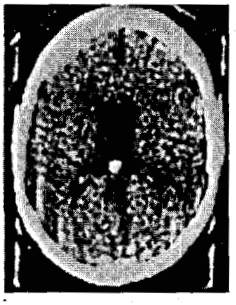


Accelerated Charged Particles Used for Tomography

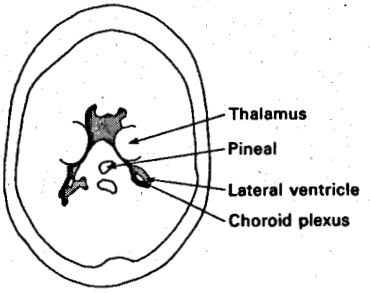


Helium ions from the 184-inch synchrocyclotron were used to explore their imaging capabilities in comparison to x-ray computed tomography by Drs. Kenneth Crowe, Ronald Huesman, John Cahoon and Thomas Budinger (whose brain image is shown for x-rays and a very low dose of helium ions). Neon ions have recently been used by Drs. Tobias and Fabrikant.

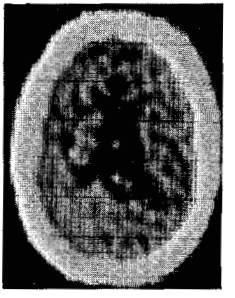
EMI



1600 mrad
180 VIEWS

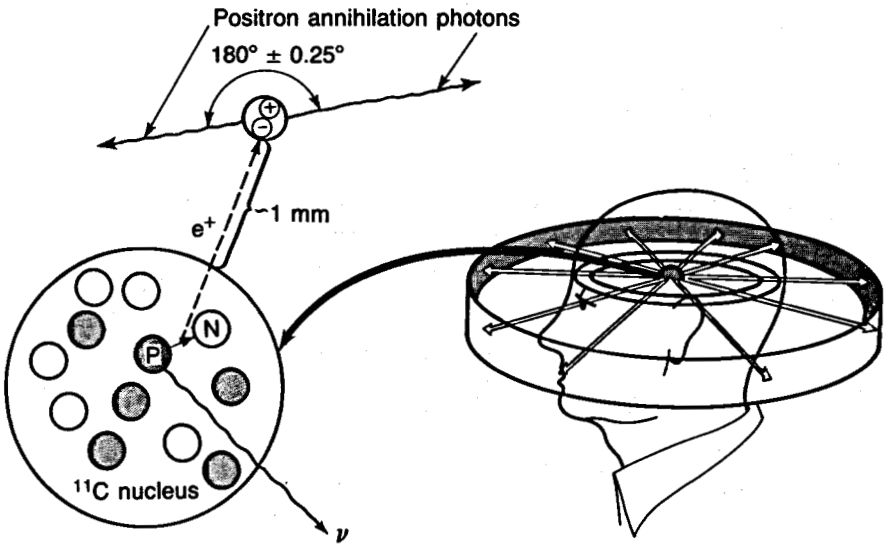


HELIUM IONS



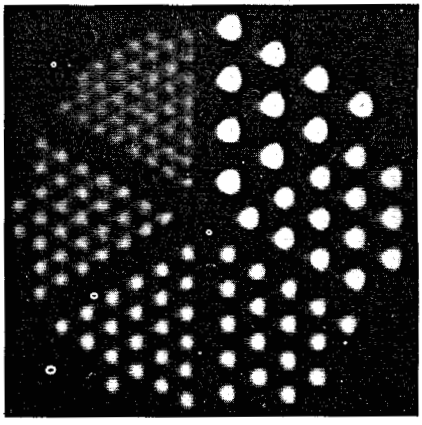
30 mrad
64 VIEWS

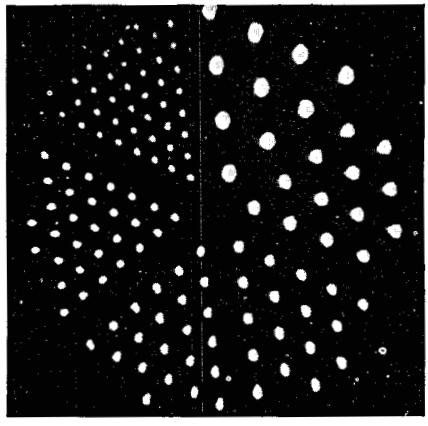
Positron Tomography

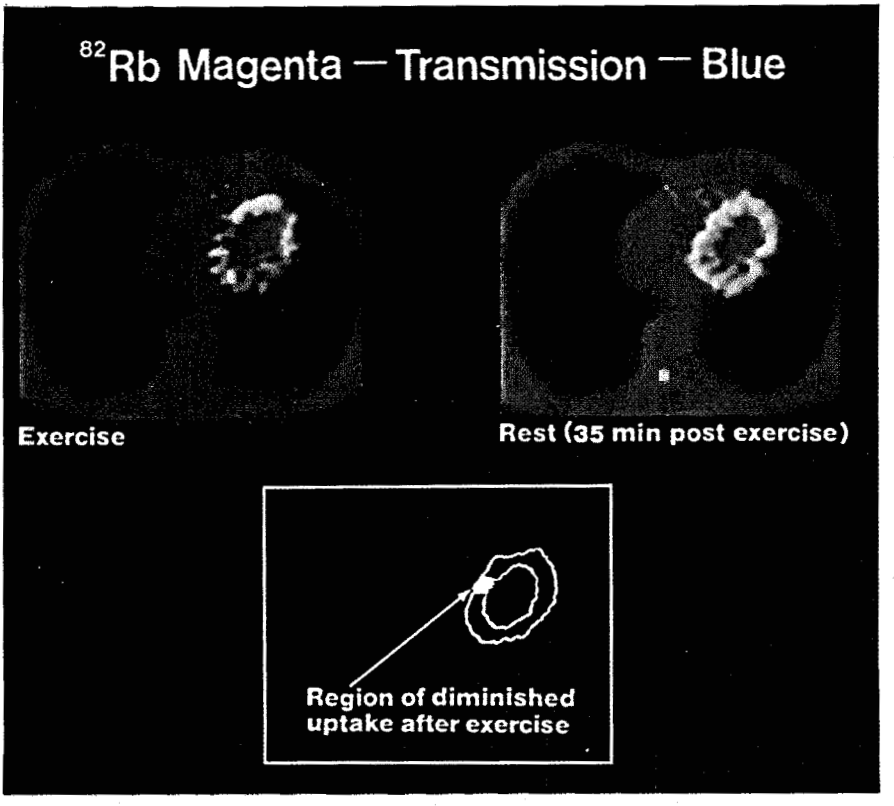


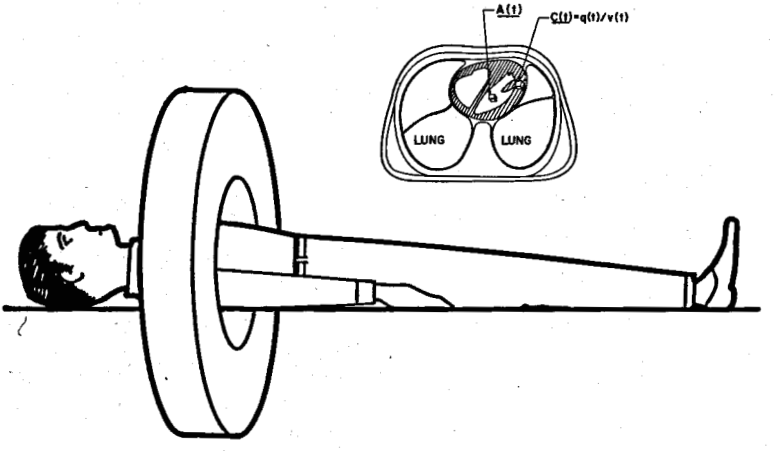
The first positron camera was produced by H.O. Anger in the late 1950s. The first fully dynamic positron emission tomograph using a circular array of crystal detectors was developed in 1978 by Drs. Stephen Derenzo, Ronald Huesman, Thomas Budinger, and Mr. John Cahoon and Tony Vuletich. PET studies focus mainly on understanding in vivo biochemistry in health and disease.

By 1986 tomograph technical developments led to the highest resolution system able to resolve small nervous system nuclei associated with specific functions (2.3 mm).

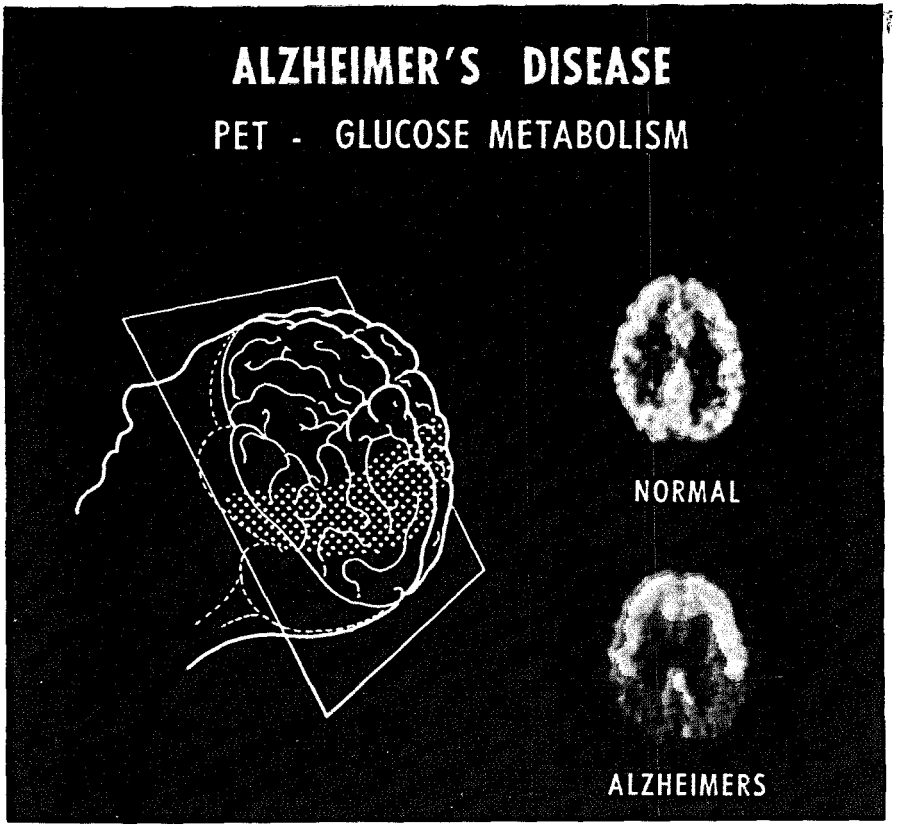




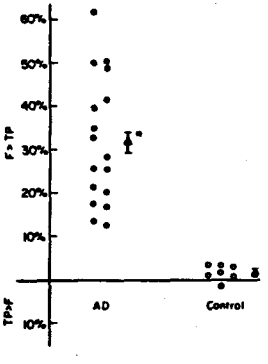




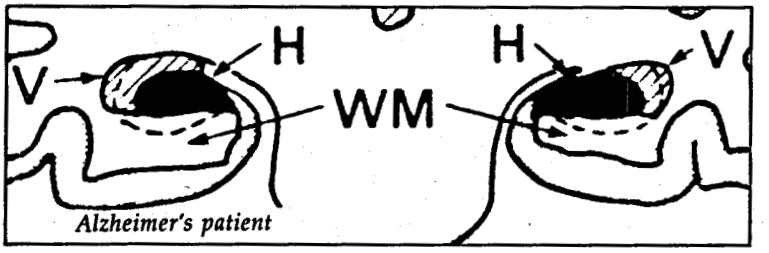
A new method of noninvasive evaluation of heart muscle perfusion using PET was developed by Dr. T. Budinger and Y. Yano. Using conservation of mass principles, flow is determined from the PET measurements ($F \propto C(T)/\int A(t)dt$).



Studies of aging commenced in the late 1940s when Dr. Hardin B. Jones observed that the clearance of radioactive gas was decreased with increasing age. It was not until 1980 that we were able to relate specific patterns of brain metabolism (below) and hippocampal anatomy changes (right) to Alzheimer's dementia using PET and NMR respectively.

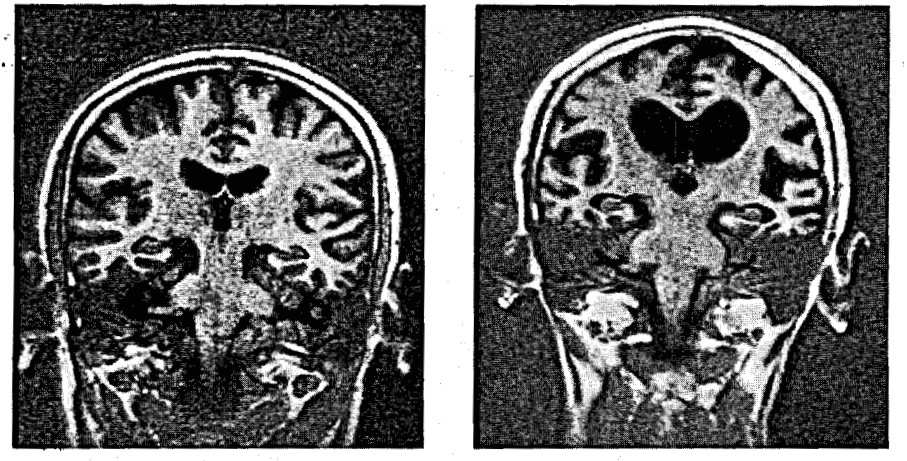


The decrease in brightness in the parietal and temporal (TP) cortical regions of the Alzheimer's brain reflects a decrease in glucose metabolism of 30% relative to the frontal lobe cortex in studies by Dr. Robert Friedland and others.

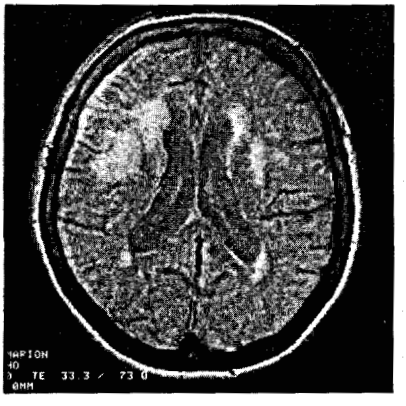


Pattern of hippocampal atrophy: Solid area represents atrophic hippocampus. Dashed line is outline of normal hippocampus. H=hippocampus. WM=white matter. V=ventricle.

Normal **Alzheimer's**

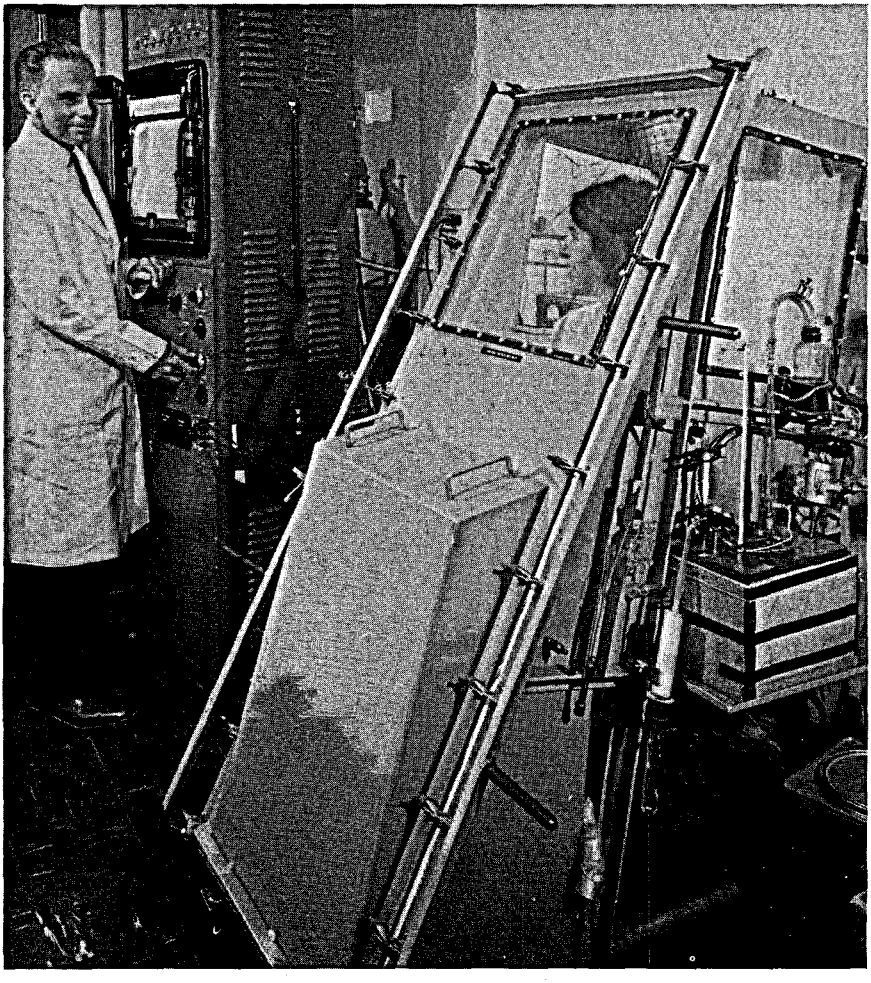


NMR proton density images detect atrophy in the hippocampal areas of Alzheimer's patients being studied by Drs. William Jagust, Phillip Seab, Mark Roos and Sam Wong. These regions of the brain are associated with memory.



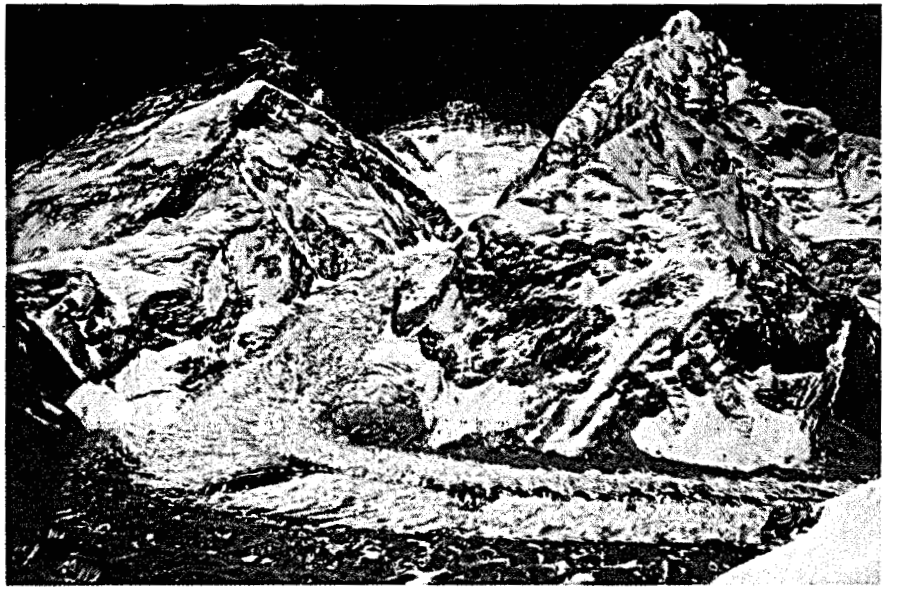
Abnormal lesions in the white matter of the brain in 30% of the non-demented population over 60 years of age are under intensive study by Drs. Peter Valk and Craig Van Dyke.

Body Composition Studies

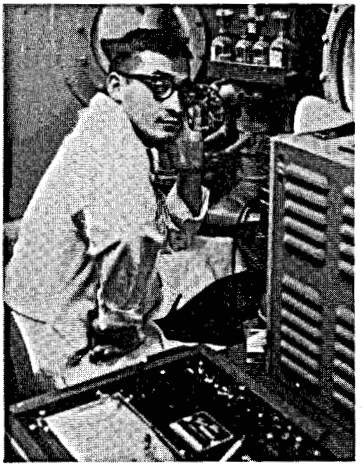


The "Helium Chamber," developed by William Siri, provided a passive procedure for accurately determining body density. Combined with oral administration of a trace of tritium labeled water, accurate measures of total body water, fat, protein, and bone mineral were obtained for patients seen at Donner Laboratory and in extensive studies of healthy subjects by age, sex, and other parameters.

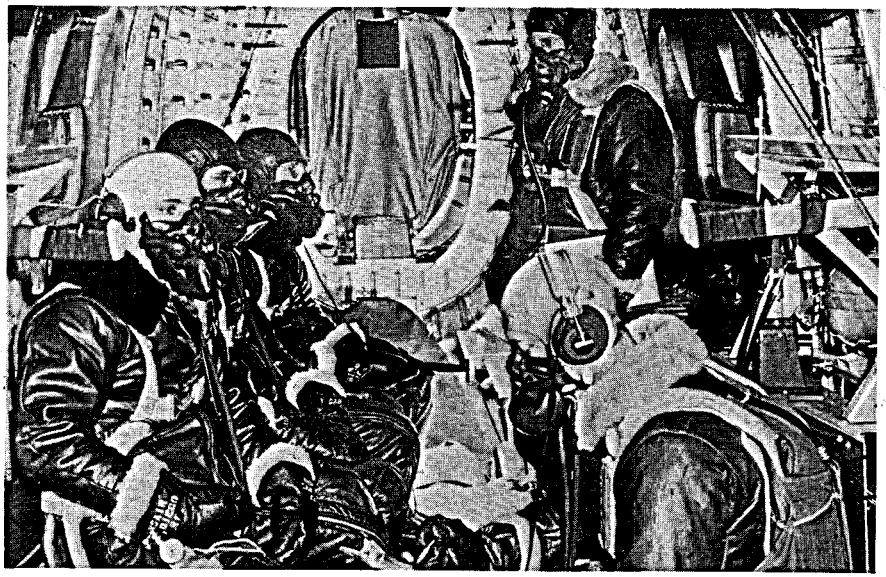
High Altitude Physiology

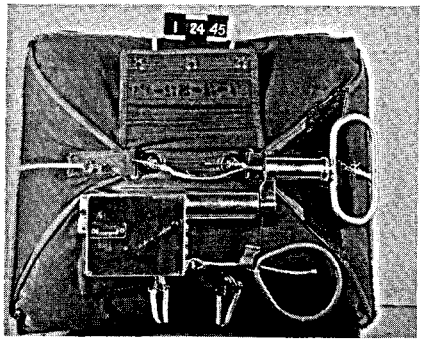


The physiology of the bends from high altitude exposures during World War II was studied by Drs. Lawrence, Hardin Jones, and Cornelius Tobias. Later the response of the hematopoeitic system to oxygen pressure was studied in the Donner high altitude chamber by Wil Siri (who was a principal leader in the 1963 Mt. Everest Expedition and is shown here at a simulated altitude of 17,000 ft for 4 days) and by Drs. Winchell and Donald Van Dyke.

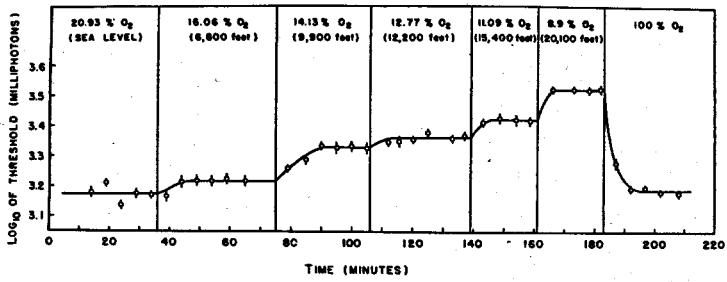


Aviation Medicine

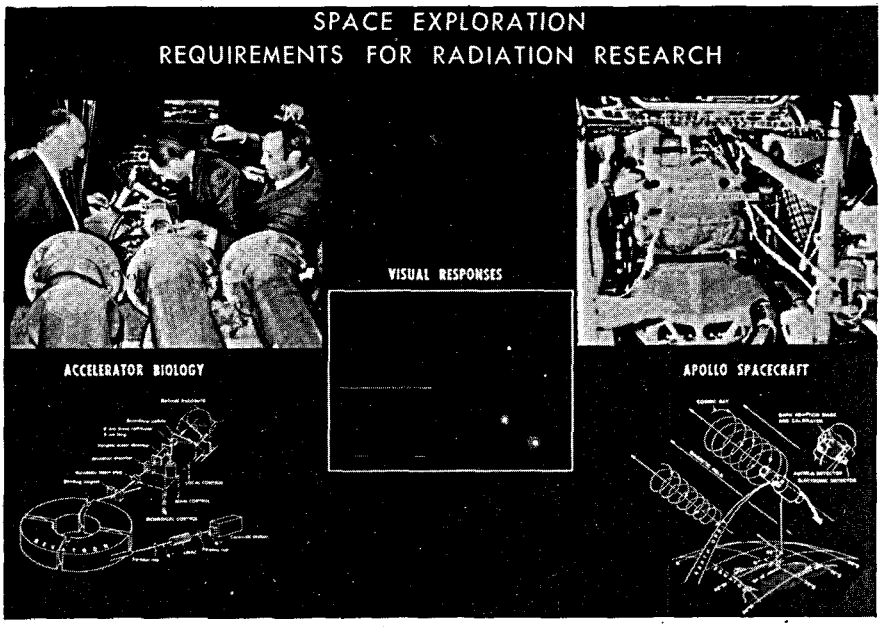




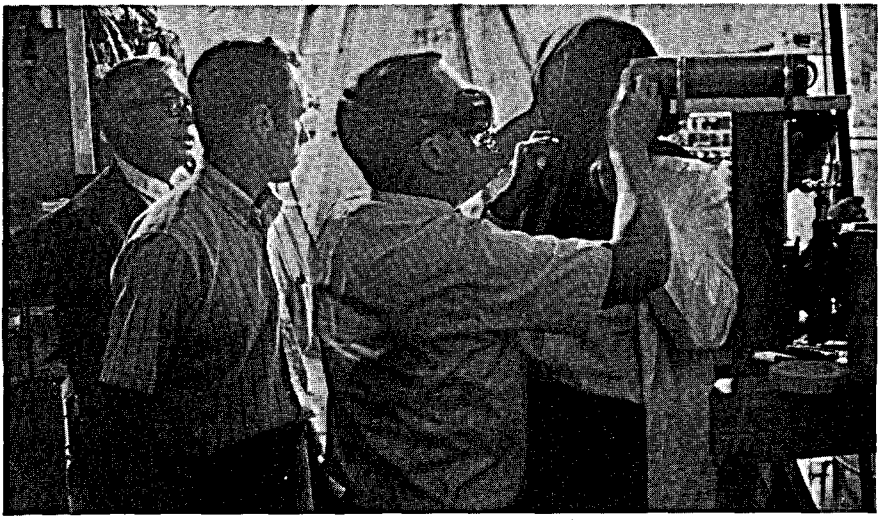
During WWII systems to ensure the integrity of O_2 supplies in aircraft were invented by Dr. Tobias who also invented an automatic parachute release with Donner scientists. The Donner group, including Drs. Hardin Jones and John Lawrence, studied the effects of low O_2 on physiology and discovered the anesthetic properties of xenon gas.



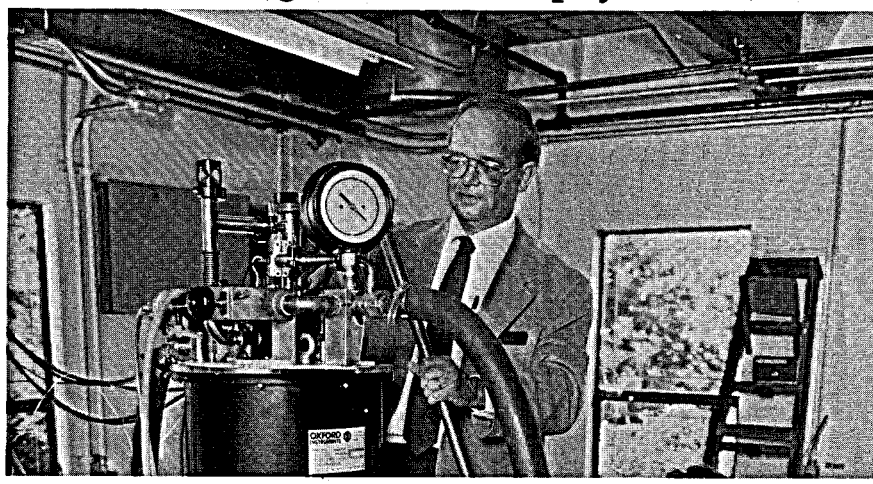
The effect of progressive degrees of oxygen-lack on visual thresholds. A rise in threshold denotes a decrease in visual acuity.



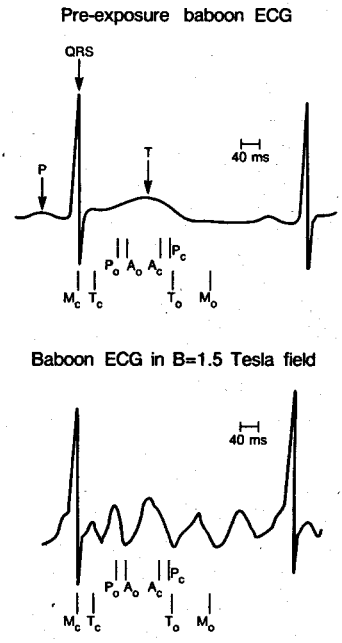
Observations of light flashes similar to those shown under "visual responses" (above) by astronauts on Apollo missions to the Moon led to experiments by Drs. Tobias and Budinger which demonstrated cosmic particles (protons, helium, carbon, nitrogen, and oxygen ions) were responsible for the light flashes. In the first experiment dark-adapted Dr. Tobias is positioned in a 640 MeV neutron beam (only a few particles) by Budinger, with Drs. Lyman and Born checking the dosimetry. *Above:* Dr. Edward McMillan is positioned to make the first observations of accelerated nitrogen ions.



Magnetic Field Biophysics

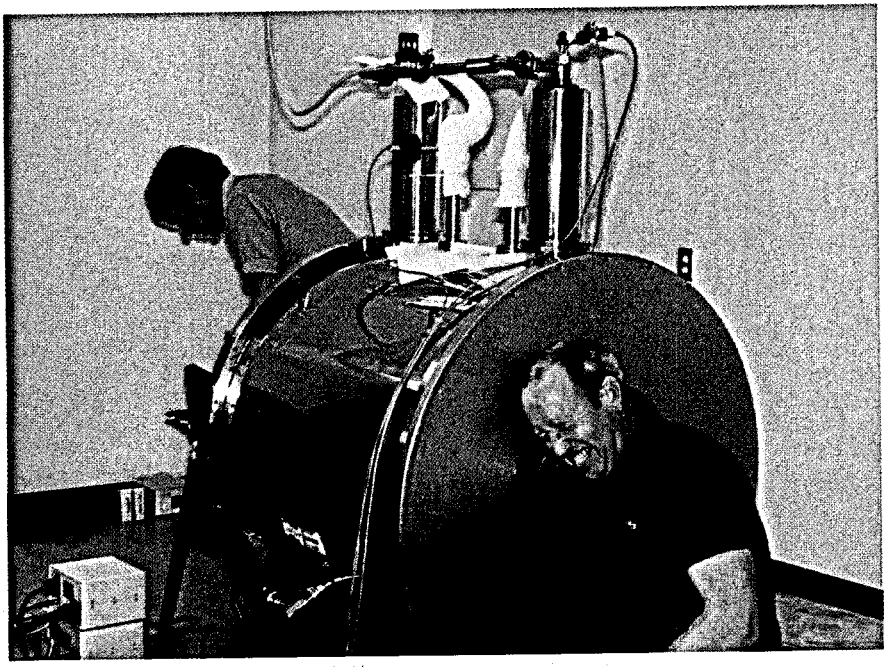


Above: A 9 Tesla (90,000 Gauss) superconducting magnet that was custom-made by Oxford Instruments, Inc., for LBL research. Drs. Tom Tenforde, Con Gaffey, and Robert Liburdy study the effects of magnetic fields on membranes, nerve bioelectric properties, and cardiovascular dynamics. The conformation of macromolecules using magnetic circular dichroism can also be pursued using this system.

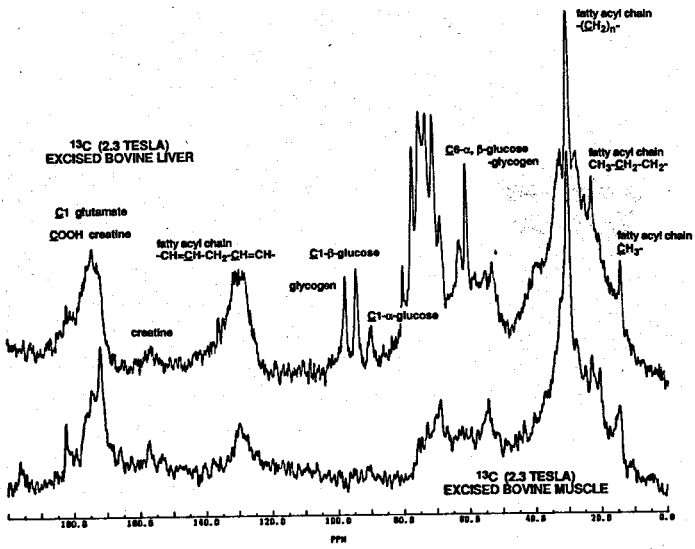


Right: Electrocardiograms recorded from a baboon before and during exposure to a 1.5 Tesla static magnetic field. The electrical potentials studied by Drs. Con Gaffey and Tom Tenforde are generated during pulsatile blood flow in the presence of a magnetic field. Vertical bars denote the times of opening (subscript "o") and closing (subscript "c") of the mitral (M), tricuspid (T), pulmonary (P), and aortic (A) valves.

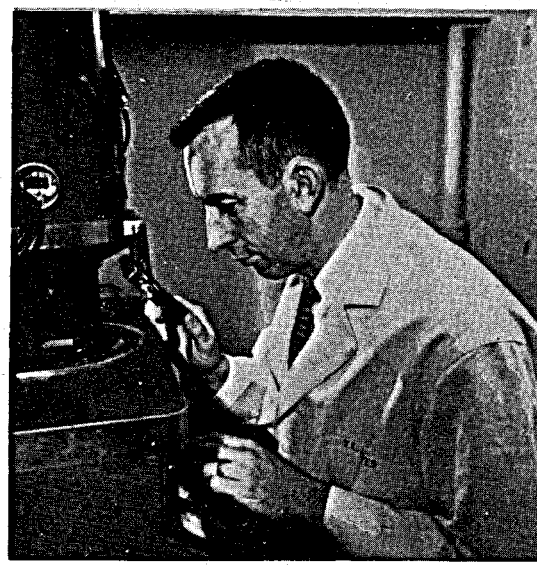
Tissue Studies by NMR Spectroscopy



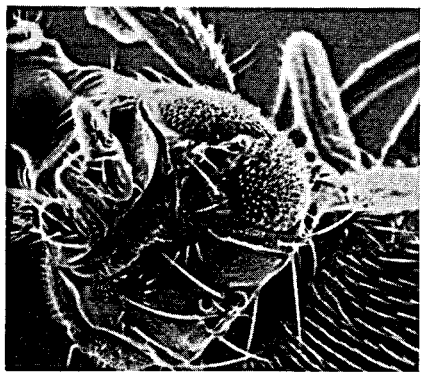
Above: Exercise physiology study of energetic metabolism by phosphorus-31 NMR by Dr. T.F. Budinger. *Below:* Carbon-13 NMR spectra of animal tissues studied by Nicholas Bolo and Drs. Richard Newmark and Mark Roos.



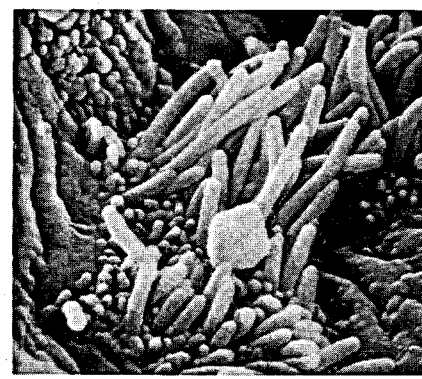
Structural and Morphological Biology



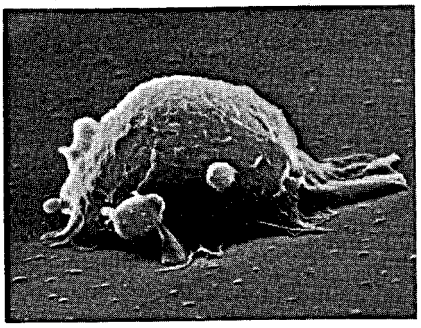
Early studies in transmission EM and scanning electron microscopy (secondary electrons) started by Donner scientists (Drs. Thomas Hayes and Robert Glaeser) in 1950 and 1965, respectively.



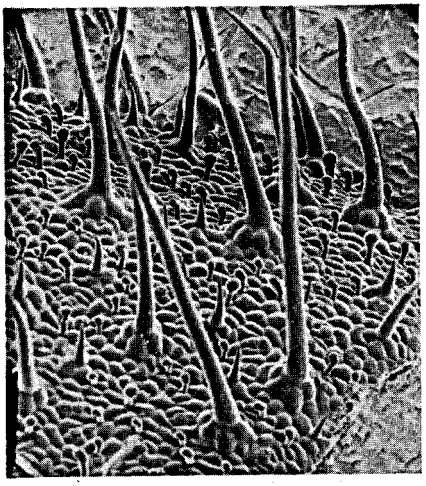
First living fruit fly head (about 0.7 mm) imaged by the reflection scanning electron microscope. Purpose was to determine phenotype in genetic studies.



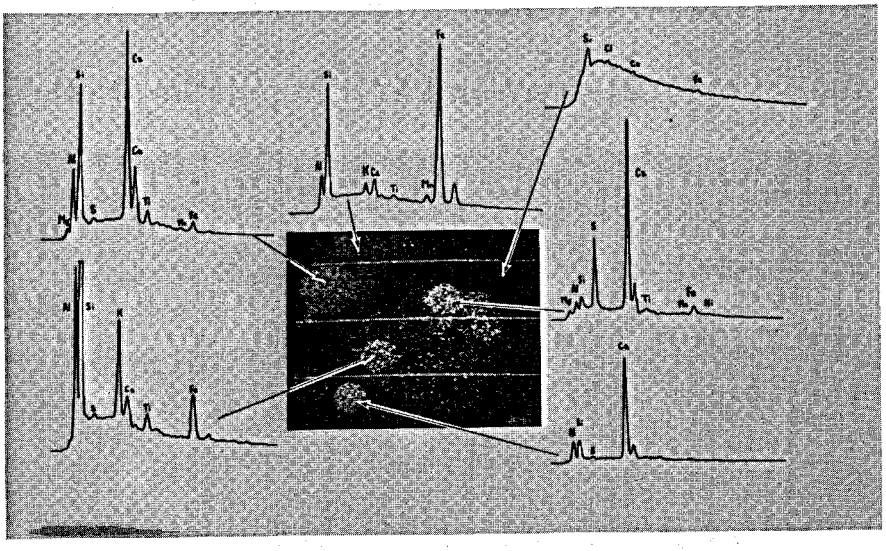
Hydrated (quick-frozen) sample of the surface cells of Pelargonium. This visualization allows selection by micromanipulator of subcellular parts for analysis of chemical composition.



Macrophage from the lung ingesting pollutant particles.

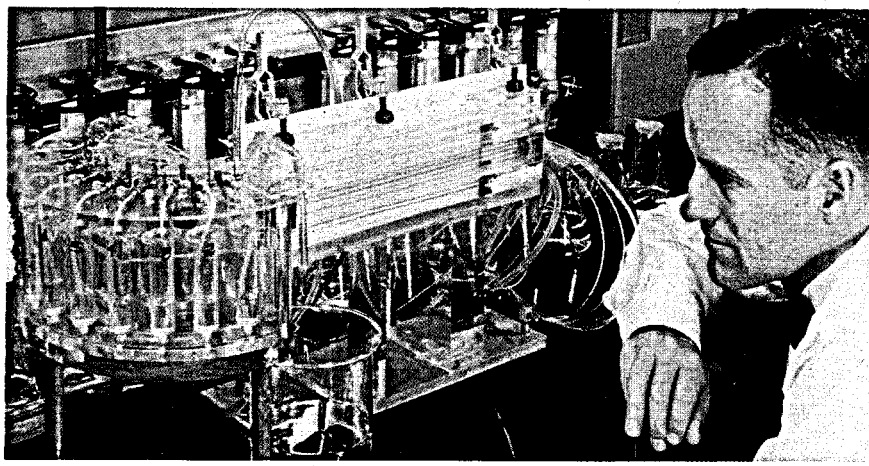


Ciliated cell of the lung airway with a trapped pollutant particle.



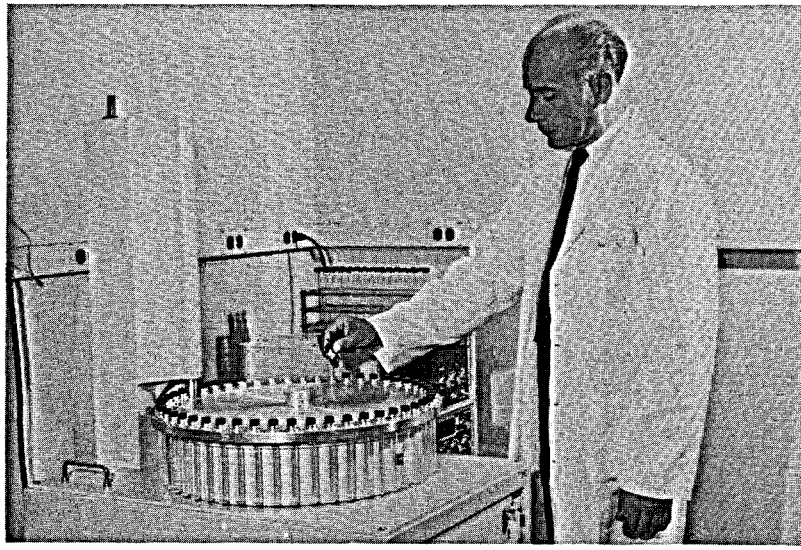
Analysis of the shape and elemental composition of pollutant particles is accomplished by characteristic x-ray emission induced by the electron beam of the scanning electron microscope.

Separation of Biological Units Using Their Biophysical Properties



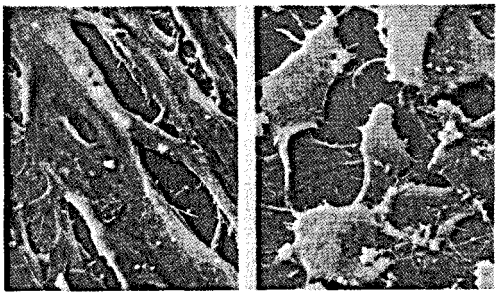
Dr. Howard Mel and his unique stable-flow (STAFLOW) free boundary migration and fractionation system.

Radioimmune Assay and Erythropoietin Studies

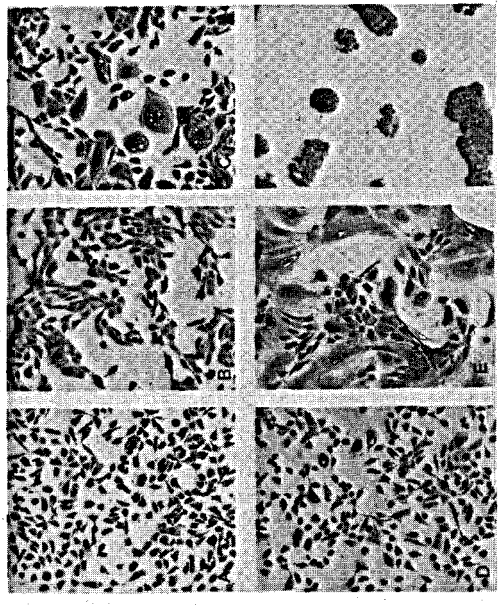


Drs. Joseph Garcia, Jack Schooley, and Donald Van Dyke developed the first antibody to erythropoietin and Drs. Garcia and Gisela Clemons developed the radioimmune assay.

New Cell Biology



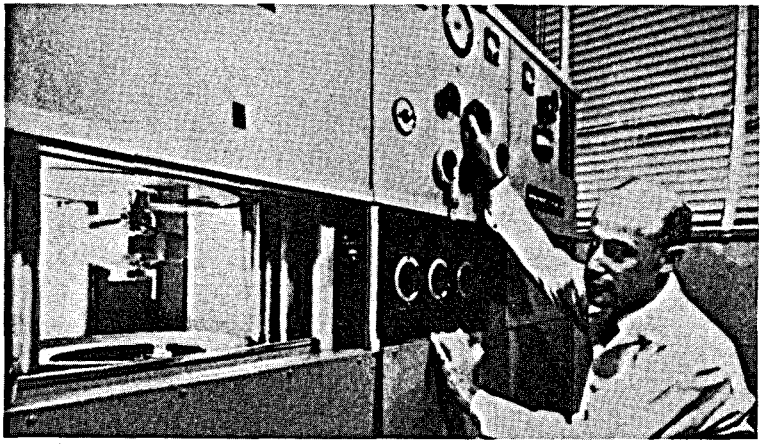
Scanning electron micrographs show normal cells removed from the body walls of a 10-day-old chicken embryo and grown in culture (left). When infected with Rous sarcoma virus by Drs. Mina Bissel and David Dolberg, the cells become malignant (right). This transformation does not occur inside an embryo, clearly indicating an interaction between the stage of development and the induction of cancer.



Drs. Martha Stampfer and Jack Bartley

Carcinogenic transformation in human epithelial cells in culture was first demonstrated by Drs. Stampfer and Bartley by treating normal human breast cells (Panel A) with benzo(a)pyrene, an ubiquitous environmental carcinogen. This treatment first produced widely heterogenous cultures with extended life spans (Panels B and E). Two immortally transformed cell lines with distinctly different morphological and biochemical properties (Panels C and F) were isolated from the two types of extended life cells.

Lipoproteins and Coronary Artery Disease



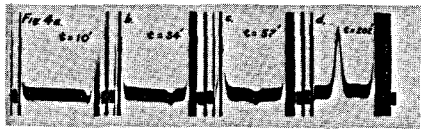
In 1948 Drs. John Gofman, Frank Lindgren, and Harold Elliot started studies of lipoproteins using the ultracentrifuge invented by Svedberg in 1924. Studies of anomalous patterns in the migrating boundaries detected by optical systems resulted in the delineation of the major lipoprotein components in the human plasma.

The Role of Lipids and Lipoproteins in Atherosclerosis

John W. Gofman, Frank Lindgren, Harold Elliott, William Mantz, John Hewitt, Beverly Strisower, and Virgil Herring

Division of Medical Physics, Donner Laboratory, and the Radiation Laboratory, University of California,[1] Berkeley, and Thomas P. Lyon, *San Jose, California*

SCIENCE, February 17, 1950



The first biomedical application of the lipoprotein quantitative methodology developed by Drs. Gofman and Lindgren was to the major health problem, atherosclerosis and coronary artery disease. They identified the actual macromolecules that increased in concentration with the development of experimental atherosclerosis in the rabbit and these studies focused the world's attention on the influence of cholesterol and lipoprotein patterns in coronary artery disease.

Dietary Prevention and Treatment of Heart Disease

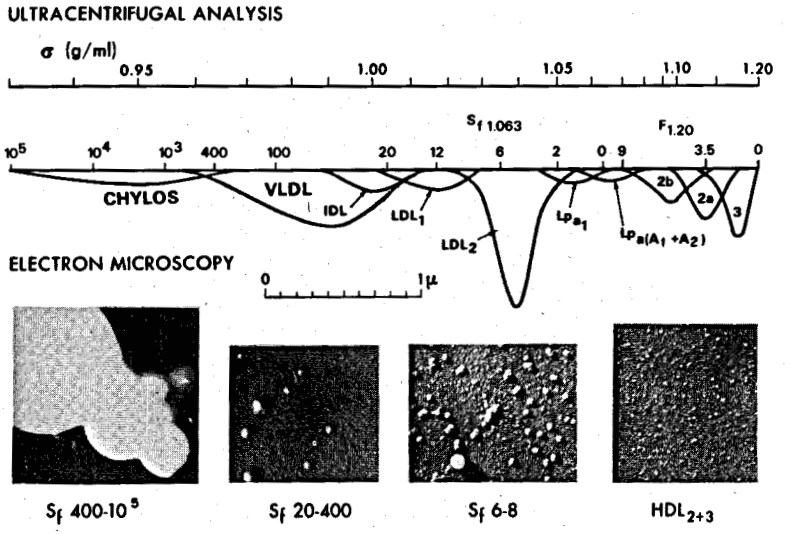
by **JOHN W. GOFMAN, Ph.D., M.D.**
Donner Laboratory, University of California, Berkeley

ALEX V. NICHOLS, Ph.D.
Donner Laboratory, University of California, Berkeley

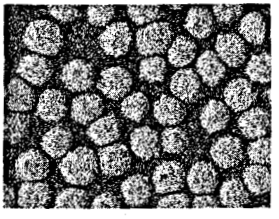
E. VIRGINIA DOBBIN,
Senior Dietitian, E. V. Cowell Memorial Hospital, University of California, Berkeley

New York **G. P. PUTNAM'S SONS**

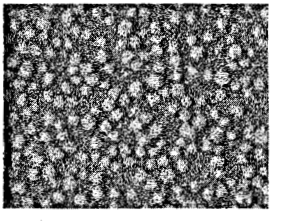
1958



The major lipoprotein categories discovered at Donner are the subject of continuing studies on the subclass patterns in relation to genetic diseases by Drs. Ronald Krauss and Melissa Austin.

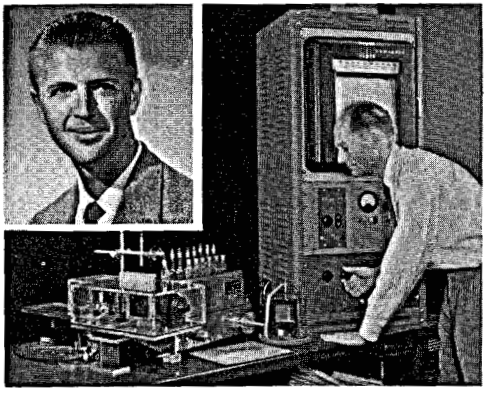


"Bad"



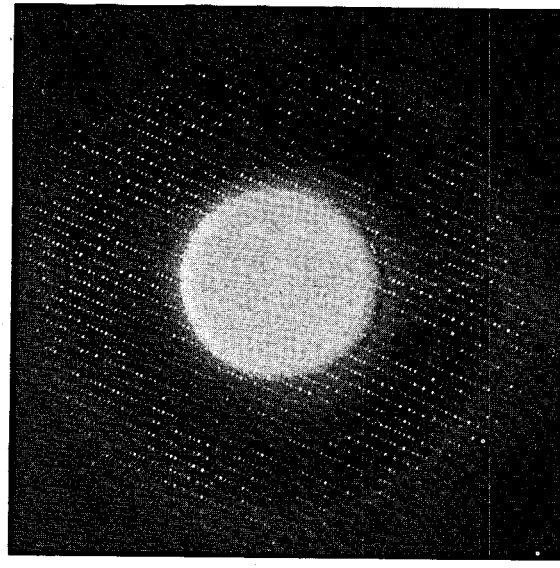
"Good"

Electron microscopy by Dr. Trudy Forte played the lead role in visualizing the structure of low density ("bad") and high density ("good") lipoproteins.

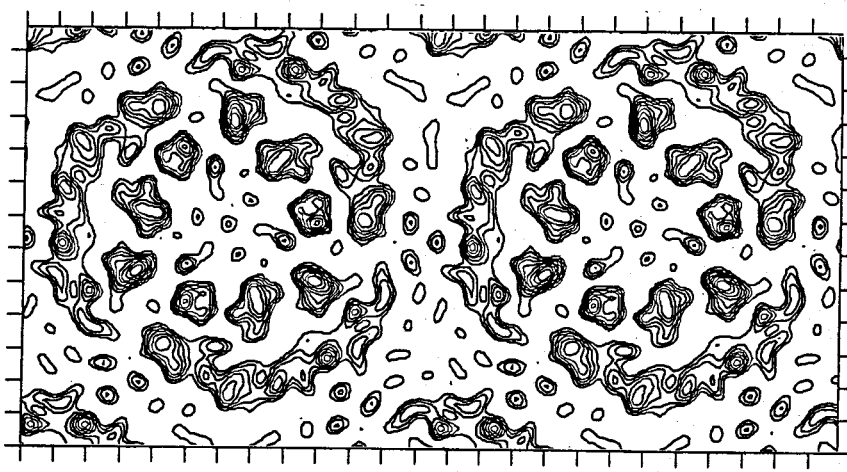


Biochemistry studies led by Dr. Alex Nichols with Keith Freeman are characterizing the lipids and lipoprotein biochemistry.

Structural Membrane and Molecular Biology

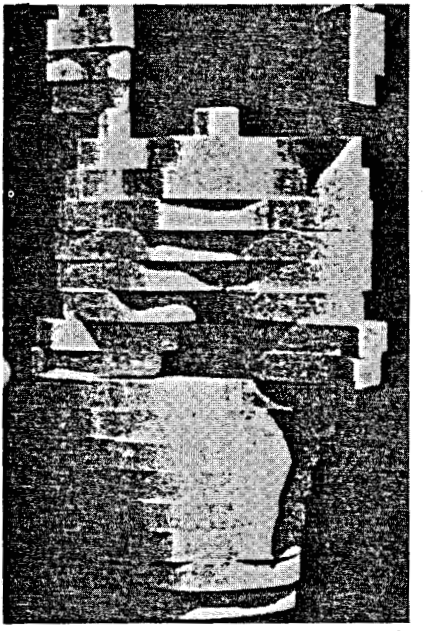


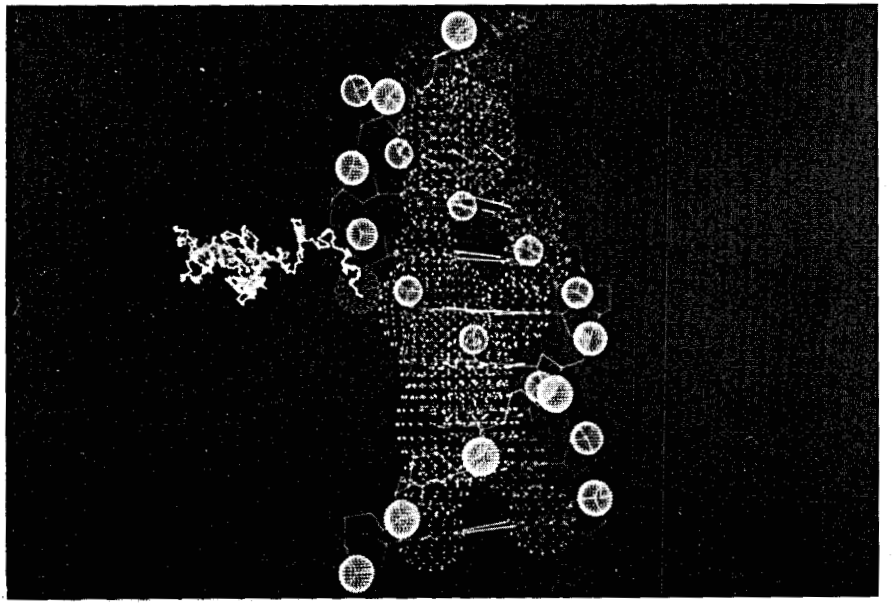
Electron diffraction pattern of crystallized protein catalase is the first demonstration by Drs. Robert Glaeser and Kenneth Taylor that a protein molecule can be preserved in the vacuum of an electron microscope by a new method which allows determination of the structure at high resolution.



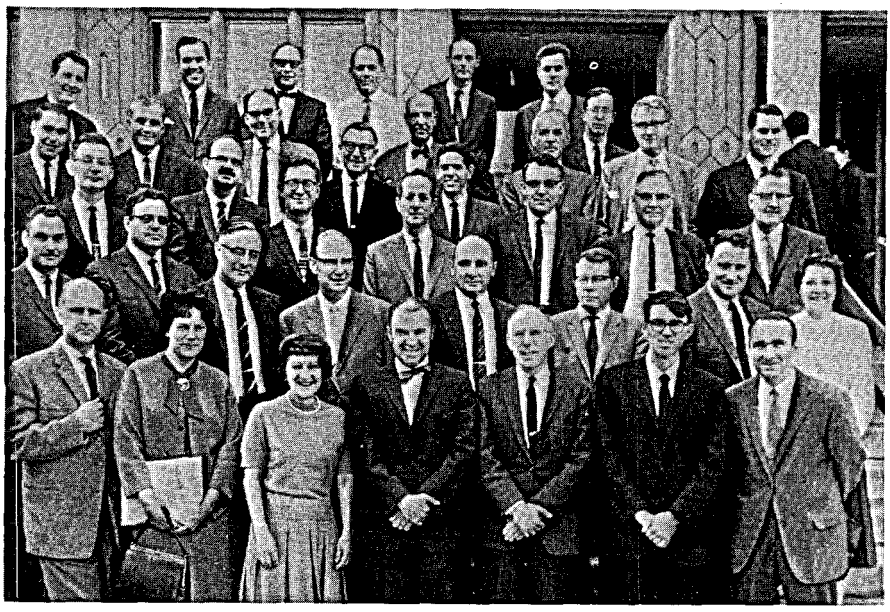
Electron density map of bacterial rhodopsin is revealed in detail by the analysis of high resolution electron microscopy images and diffraction patterns. (Work resulted from collaboration between Dr. Ken Downing of Dr. Glaeser's group and Richard Henderson, MRC, Laboratory of Molecular Biology).

A low resolution three-dimensional model of helix-stabilizing protein (gp32*I dimer) isolated and characterized by Dr. Junko Hosoda and associates. The protein itself is thought to be essential for DNA replication, recombination, and repair.

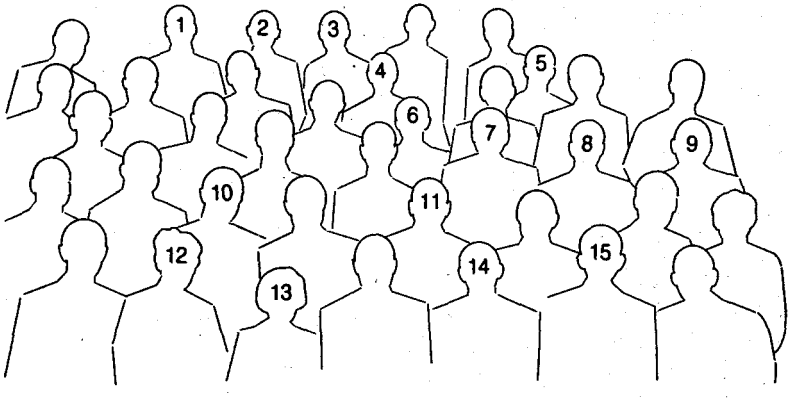




Stereochemical analysis of DNA damage by hydroxyl radicals studied by Dr. Aloke Chatterjee using theoretical chemistry and computer graphic techniques. Hydroxl radical track produced by charged particle radiation is shown approaching a "sphere of certain damage." Spheres around DNA stick model represent size of the regions sensitive to chemical attack.

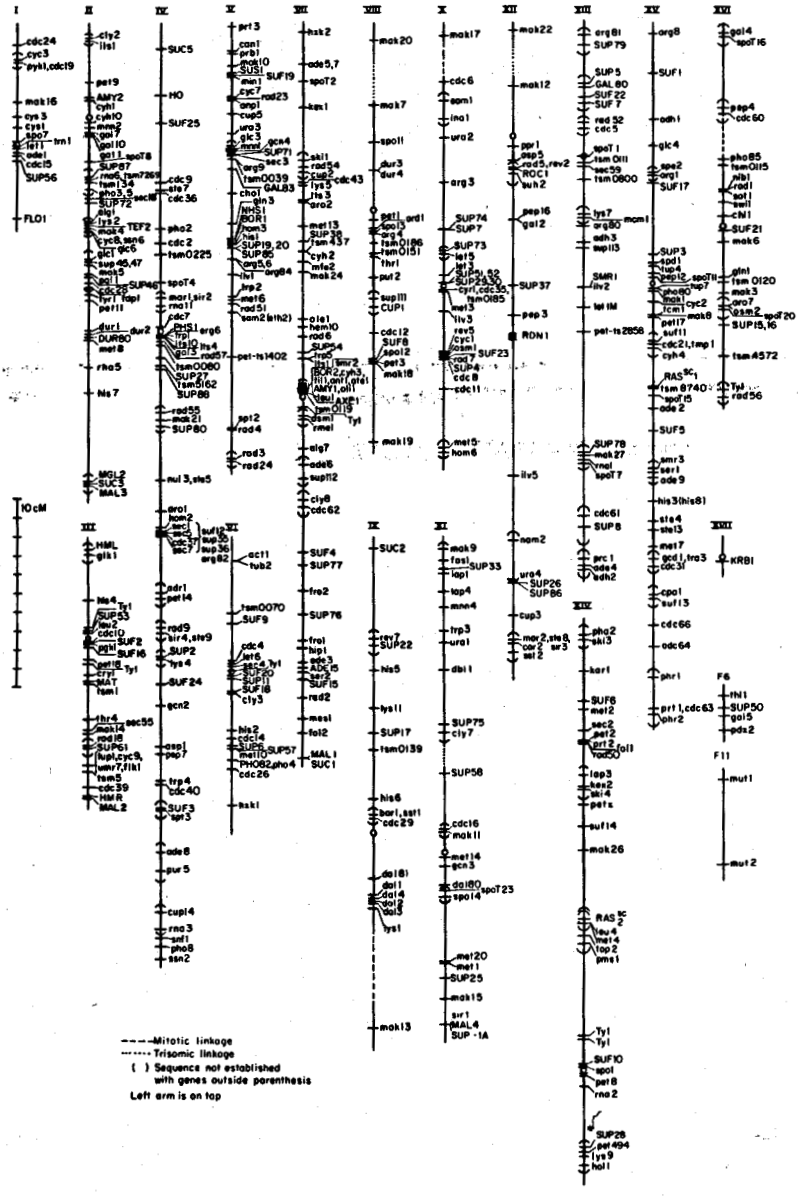


A photograph of attendees at the first meeting on DNA repair held at the University of Chicago in the 1960s. The identified individuals have either been in Donner Laboratory (1,3,5,7,8,15) or have had important interactions with Drs. Robert Mortimer, Cornelius Tobias, and others at the Donner Laboratory.



1. Bob Haynes
2. Henry Kaplan
3. Paul Howard-Flanders
4. Ernie Pollard
5. Reginald Deering
6. Howard Adler
7. Robert Mortimer
8. Raymond Zirkle
9. Donald Hawthorne
10. Dick Kimball
11. Sheldon Wolff
12. Evelyn Witkin
13. Ruth Hill
14. Richard Setlow
15. David Freifelder

Genetic Map of S. cerevisiae



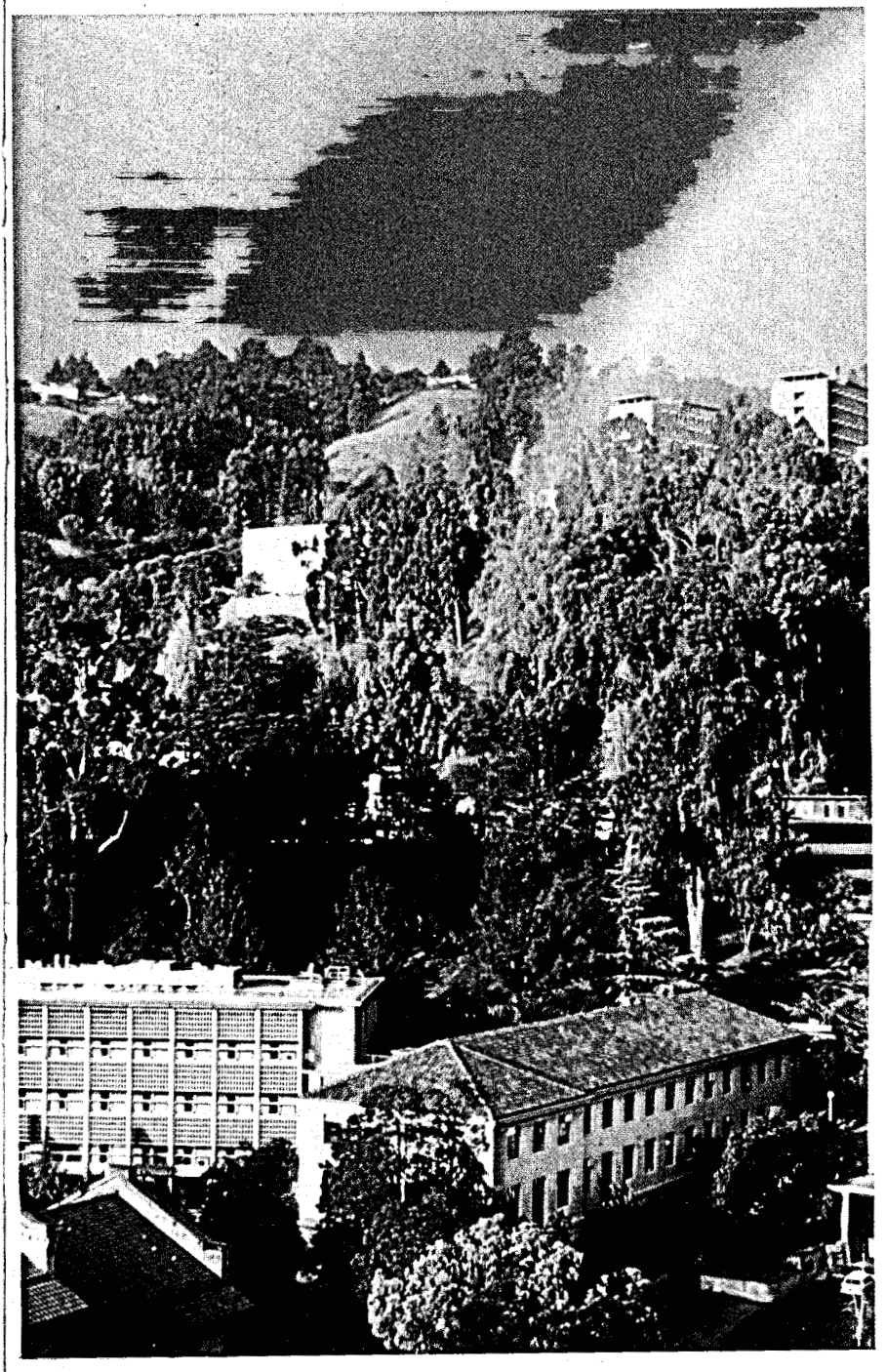
From the early work by Dr. Robert Mortimer using yeast to study genetic mechanisms in 1959 has evolved methods and knowledge responsible for major advances in yeast and human genetics.

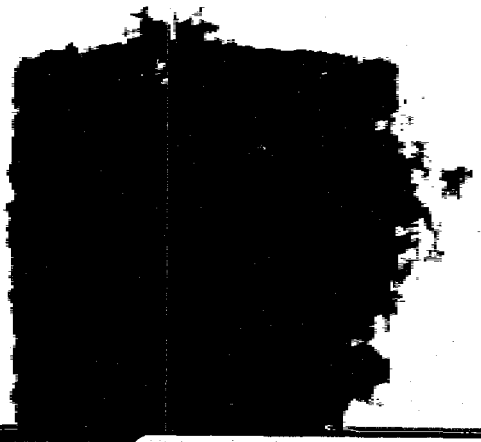
The Next Fifty Years

The current research areas of Donner Laboratory and the Division of Biology and Medicine of the Lawrence Berkeley Laboratory are expected to grow, with new emphases stemming from integration of mathematical, physical, chemical, and biological techniques discovered and implemented over the past fifty years. The research efforts range from the development of radiotracers and accelerated heavy ion beams for human physiology and disease treatment to cellular and molecular biology and genetic deciphering of the human genome.

The objectives are to explore relationships between genetics, macromolecular composition, cellular patterns and organismal form and behavior.

Right: Photo by Dr. Paul Bartlett of UC Berkeley





ABOUT THE FRONT COVER: Drawing of original Donner Laboratory in 1941 before addition in 1954 (pg. 60).

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PUB-628/10/87/2m