Nuclear Medicine

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Chapter Eighteen

The Birth and Development of Nuclear Physics: 1895–1929

The current use of radionuclides in the diagnosis and treatment of disease has evolved from the personal and scientific interaction of chemists, physicists, physicians, biologists, engineers, physiologists, biochemists, pharmacologists, and others. Today's functional and molecular nuclear medicine has developed from George Hevesy's "indicator" method that made it possible to trace and measure the living movement of atoms or compounds in the fluids, organs, and tissues of the body. In turn, his use of radioactive tracers depended upon the development of nuclear physics that, stimulated by a discovery by a German physicist, confirmed in 1913 the nuclear structure proposed a century earlier by a clinical pathologist.

In late 1895 Wilhelm Röntgen was intrigued by the fluorescence of a barium platinocyanide screen lying near a charged Crookes tube whose glass wall luminesced where struck by the electron stream. Since he had completely enclosed the tube within light-tight black cardboard, he tested whether the fluorescence of the crystals was due to the luminescence of the tube. In the completely darkened room the crystals fluoresced despite the absence of any visible rays. His studies then demonstrated that these unknown invisible "X" rays ionized the surrounding air, imaged fluoroscopically the bones of his interposed hand and other dense objects, and sensitized photographic emulsions to image interposed dense objects. The French physicist Antoine Henri Becquerel, leading authority on fluorescence, assumed that the fluorescence of the glass had produced the X rays (Fig. 18.1). He was pleased to demonstrate that uranium nitrate rendered fluorescent by sunlight also generated rays that would penetrate opaque paper and sensitize photographic plates. After he interposed a copper cross, this experiment was delayed for several days by cloudy weather. In frustration, Becquerel developed the plate as a control, nevertheless. He was astonished to see the plate darkened just as though the uranium had fluoresced after exposure to bright sunlight. In addition, there was a brilliant white image of the copper cross. These "Becquerel rays" were even more puzzling than Röntgen's X rays. The energy emitted by the latter was clearly derived from the energetic stream of electrons,
but what was the source of the energy emitted by these rays? Becquerel had excluded every external source of energy from his uranium. Yet all scientists, including Becquerel, refused to accept the seeming spontaneous generation of energy that would break the law of conservation of energy. One of his graduate students at the Ecole Polytechnic, however, would soon convince the disbelievers.

Marie Sklodowska Curie, after the birth of her daughter Irène in September 1897, began her doctoral thesis by investigating her professor’s discovery, which she termed the radioactivity of uranium. Fortunately, her husband, Pierre Curie, also a physics professor at the Ecole, had invented the quartz piezo-electroscope. Much more sensitive and precise than the gold-leaf electroscope, this instrument could measure accurately the very small electrical currents generated by radiation that the English physicist J. J. Thomson (1856–1940) had reported. Marie’s initial results were so promising that Pierre joined her on the trail of radioactivity (Fig. 18.2). Enthusiastically working day and night with thousands of pounds of pitchblende, an ore known to be radioactive, she chemically extracted by trial and error for radioactivity. A new element, by weight seven hundred times more radioactive than uranium, was isolated in July 1898 and named polonium for Marie’s native Poland. Another new element, named radium, a million times more radioactive than uranium, was isolated in December 1898. Becquerel was given a pinpoint sample of radium in a glass vial, which he demonstrated would radiate light, heat, and ionizing radiation that did not diminish over time. It also reddened the skin under the vest pocket in which he carried the sample. Curie shared the 1903 Nobel Prize for physics with her husband and with Becquerel and later would receive the 1911 Nobel Prize for chemistry. The disbelievers were convinced—but what was the scientific explanation for natural radiation?

Meanwhile, English physicists had begun to characterize the constituents of the atom and its radiation. J. J. Thomson at the Cambridge Cavendish Laboratory in 1897 measured the mass of the negatively charged “corpuscles” in the cathode ray beam to be approximately 1/1,800 the mass of hydrogen, previously thought to be the smallest particle of matter. Busy with the electron, Thomson assigned the investigation of Röntgen’s X rays and Becquerel’s rays to his first assistant, Ernest Rutherford (Fig. 18.3). Before leaving in 1898 to head the physics laboratory at McGill University in Montreal, Rutherford wrote, “...there are present at least two distinct types of radiation—one that is very readily absorbed, which will be termed for convenience the Alpha radiation, and the other of a more penetrating character, which will be termed the Beta radiation.” He also noted that thorium radiation was more energetic and penetrating than uranium radiation. At McGill Rutherford and Owen demonstrated in 1899 that thorium emitted a radioactive gas with a “half-value period” (shortened to “half life” in Berkeley during the 1930s) of about one minute and derived the familiar decay formula for the intensity of radiation at any time:
\( I_t = I_0 e^{-\lambda t} \), where the decay constant \( \lambda = 0.693 / T_{1/2} \). Rutherford's analyses of various uranium and thorium samples led to the radical statement: "...the radioactive elements must be undergoing spontaneous transformation," which unfortunately echoed the ridiculed alchemists' term "transmutation."

Hans Geiger (1882-1945) was the senior physics laboratory assistant who greeted Rutherford in 1906 upon his arrival at Owens College in Manchester. This remarkably productive pair announced in 1908, "The alpha particle after it has lost its positive charge is a helium atom." By 1911 the Manchester Laboratory had become the preeminent training and research center for atomic physics, with C. T. R. Wilson (1869-1959) photographing ion tracks in his cloud chamber and with many graduate students, including Bohr, Hevesy, Fajans, and Moseley. The Rutherford atom of 1911 was composed of a positively charged nucleus that contained almost all its mass surrounded by a cloud of negatively charged electrons. It was completed in 1913 by the Niels Bohr (1885-1962) theory of specific orbital electrons in quantum states, consistent with the quantum theory of Max Planck (1858-1947) published in 1900. The chemistry of an element was determined by the orbital structure of its electrons, while an element's nuclear structure determined its stability or radioactivity. At this time Rutherford, Soddy, the Curies, and Villard identified three radioactive nuclear emissions: alpha particles consisting of doubly positive charged helium nuclei, beta particles consisting of negatively charged electrons, and nonparticulate gamma rays consisting of highly penetrating electromagnetic radiations.

The year 1913 also witnessed the proof of a hundred-year-old hypothesis made by the clinical pathologist William Prout (1785-1850). After accurately remeasuring the proportional weights of the elements, in 1815 he published the prophetic whole number rule, stating that the weights of all elements were multiples of the atomic weight of hydrogen. Using X-ray spectrometry, H. Moseley (1887-1915) confirmed Prout's whole number rule by demonstrating the integral "staircase" order of increasing hydrogen nuclei, i.e., protons (Z) of the eleven elements Ca (Z=20) to Zn (Z=30). The staircase of elements was greatly extended in 1920 by F. Aston (1877-1945) using his mass spectograph. After World War I Rutherford in 1919 first induced transmutation by bombarding nitrogen with radium alpha particles to form protons and stable oxygen. Gamma ray scatter by interaction with electrons was described by A. Compton (1892-1962). During the next five years M. Born (1882-1970), L. de Broglie (1892-1960), E. Schrodinger (1887-1961), W. Heisenberg (1901-1976), and P. Dirac (1902-1984) refined and integrated the wave and particulate properties of particles and radiation consistent with Planck's quantum theory. In 1928 R. Millikan (1868-1953), who in 1911 had measured the negative charge of the electron, at the California Institute of Technology (CIT) demonstrated that atoms share electrons in molecular orbits. That same year Geiger invented the beta avalanche GM counter.
D."\textsuperscript{17} Certain investigations of the physical chemistry of lead could now be performed using radiolead to trace the kinetic behavior of lead.

Hevesy had devised and applied this tracer concept earlier while still a student in Geiger's introductory course. Though satisfied by the meals served at his boarding house, he suspected that the leftovers of Sunday's meat course were served later in the week. After an indignant denial by his landlady, Hevesy performed the first tracer experiment: "The coming Sunday in an unguarded moment I added some active deposit to the freshly prepared pie and on the following Wednesday, with the aid of an electroscope, I demonstrated to the landlady the presence of the active deposit in the soufflé."\textsuperscript{18}

World War I interrupted virtually all research throughout Europe. At Bohr's invitation Hevesy left Hungary for Copenhagen in 1920 to work in the Niels Bohr Institute of Theoretical Physics. Based on Bohr's theoretical assumption that the unknown element occupying place seventy-two in Mendeleev's periodic table was a homologue to zirconium (Z=40), stable hafnium (Z=72) was discovered by Hevesy and Coster in 1921 using X-ray spectroscopic analysis of purified samples obtained from minerals rich in zirconium.\textsuperscript{19} During the next three years, despite numerous publications of articles, a book on hafnium, as well as a Manual of Radioactivity with Fritz Paneth first in German and then followed by the English edition, Hevesy found time to apply his favorite idea, the "indicator" method, to fields other than analytic chemistry. During these years he performed experiments and wrote publications on the absorption and translocation of lead by plants and the circulation of bismuth (used for syphilis therapy) and lead (used in cancer chemotherapy) in rabbits and guinea pigs. These animal studies disclosed renal excretion of bismuth in the urine and hepatic excretion of lead in the feces. The study of horse bean plants with thorium B (lead-212) disclosed that "the active lead atoms are
almost completely displaced from their places in the roots by inactive atoms...." The first biological use of radioactive isotopes resulted in Hevesy's discovery of metabolic turnover.20

The isotopes of toxic heavy metals were the only available radioactive tracers in the 1920s. These were not readily applicable to medical studies. Yet two Americans, physician Hermann Blumgart (Fig. 18.5a) and physicist William Duane (Fig. 18.5b) (who had devised the radium cow in the Curie’s laboratory), safely used radium to perform the first nuclear medicine investigation in humans. Blumgart’s interest in cardiology was first stimulated when he was a student assistant in Walter Cannon’s physiology laboratory, then reinforced on the Harvard service at Boston City Hospital in 1924, and further developed during the following year spent on cardiology services in England. No one was able to measure blood flow accurately. Upon his return to Harvard in 1926 he observed the use of the radium cow for cancer therapy, with Duane measuring body radiation outside the body. Such a measurement would not disturb blood flow and could be used to time the movement of milked radon-222 ($T_{1/2} = 3.8$ days) gas from its peripheral vein injection site to its arrival at the heart and then from the heart to its arrival in a peripheral artery.

Only a few technical details needed to be worked out. Radium was very expensive, but the 20 millicurie (mCi) radium emanation tubes used for cancer therapy were obtained free from Boston’s Huntington Memorial Hospital after they were discarded at the 10 mCi level, still ample for radon injection. Radon was obtained from the sealed metal tube using a devised tube-crusher in a gas collector flask. Guided by Duane, Blumgart used a highly-charged sharp platinum Rutherford “hot wire” to collect the radon. The 2,200 volts needed to charge the platinum wire electrode were achieved by constructing twelve hundred small test tube batteries. Under
adjusted air pressure the radon clad electrode was inserted into a fine tube of hydrochloric acid which, when titrated to blood pH, became 0.1/milliliter (ml.) of radon in saline. The verified injection of the 0.1 ml. bolus was made at proper pressure in a fraction of a second with a specially designed manometer and threeway stopcock. A heavily shielded cloud chamber was devised for the arm-to-arm measurements, since the existing electroscopes could not be shielded from the patient's radioactivity. However, this detector was too heavy to be placed over the heart, so a specially designed well-shielded Geiger-type detector was devised, constructed, and used one year before the Geiger beta avalanche GM counter was invented. The Blumgart 1927 article with Soma Weiss on the measurement of circulation time in humans concluded, "Because of the simplicity of the procedure...the method is well suited to its determination in man." 2

Blumgart measured the circulation time in sixty-two normal controls. He then investigated the velocity of blood flow in physiological and pharmacological stresses, thyrotoxicosis, myxedema, anemias, polythemia, cardiovascular diseases, malignancies, and in combinations of disease and stresses. He published twenty-two articles with many collaborators between 1926 and 1951. He not only fully clarified the physiology and pathophysiology of blood flow velocity but also introduced nuclear physics, new instrumentation, and a new radiopharmacology to medicine and science. This model of clinical science was the first publication in nuclear medicine.

THE MATURATION OF NUCLEAR PHYSICS: 1930–1945

By 1930 it was clear that in order to enter the nucleus, positively charged alpha particles needed enormous energy to overcome the strongly repellant positive charge of the nucleus, the Coulomb barrier. The limitations were insulation breakdown by extremely high voltages required to accelerate particles to the required energy level and the very large space needed for the linear path.

In 1930 the American Ernest O. Lawrence (1901–1958) circumvented both problems at the University of California Berkeley (UCB) by applying an oscillating voltage to adjoining evacuated semicircular chambers for sequential acceleration of particles contained by a 4-inch magnet within a slowly widening circular path until ejected at the periphery. 2 This successful initial feasibility study of the cyclotron achieved only 80,000 electron volts (keV) protons. A quick succession of larger magnets that produced correspondingly higher energies followed: 2 million electron volt (MeV) protons and 4 to 8 MeV deuterons in 1933 from his 27-inch cyclotron, 4 to 8 MeV for many particles in 1937 with the 37-inch cyclotron, 40 MeV heavy particles in 1939 with the 60-inch cyclotron, and, at the beginning of World War II in 1942, 200 MeV for any particle with the 184-inch synchrotron (Fig. 18.6). Now it was possible to make any radioisotope and transuranics in many milliliter amounts. The first production of plutonium with the 60-inch cyclotron in 1939, as well as the catalytic letter of Einstein to President Roosevelt in the same year, were stimulated by another series of developments in Europe during the 1930s.

In 1920 J. Chadwick (1891–1974) worked with Rutherford when they surmised that nuclear emissions formed by the bombardment of nitrogen with

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Fig. 18.7 Irene (1897–1956) and Frédéric (1900–1958) Joliot-Curie.
(Courtesy of the Center for the American History of Radiology, Reston, Va.)
radium alpha particles were protons.\textsuperscript{23} In 1925 this interpretation was confirmed in the Wilson cloud chamber by photographic tracks of an alpha particle striking and remaining within a nitrogen atom, transmuting it into stable oxygen-17 and showing the tracks of the emitted positively-charged proton. A specially constructed cloud chamber by C. Anderson at CIT confirmed the 1930 prediction of P. Dirac of positron (positive beta) production by gamma rays with energy greater than 1.022 MeV.\textsuperscript{24} His 1932 photos of cosmic rays revealed positron tracks ending suddenly by electron annihilation.\textsuperscript{25} In the same year Irène and Frédéric Joliot-Curie confirmed the 1930 report of Bothe and Becker in Germany that very high-energy gamma rays were produced by polonium alpha bombardment of the light elements lithium, beryllium, and boron (Fig. 18.7).\textsuperscript{26} They estimated that 50 MeV gamma rays were emitted from paraffin bombarded by the 5 MeV alphas. Chadwick thought this impossible and repeated the experiment with multiple wave and particle detectors. His analysis of all the data concluded, "If we suppose that the radiation consists of particles of mass very nearly equal to that of the proton, all difficulties disappear. To explain great penetrating power we must assume it has no net charge...it consists of a proton and electron in close combination, the 'neutron' discussed by Rutherford in his Bakerian lecture of 1920."\textsuperscript{27}

After barely missing the discoveries in 1932 of both the neutron and the positron, the Joliot-Curies performed experiments in 1933 to detect positrons and/or neutrons by bombarding light elements with alpha particles. At the close of 1933, on New Year's Eve, the couple left their laboratory after bombardment of a target with a beam of alpha particles that entered the cloud chamber through an aluminum window. Suddenly they were called back to the laboratory by their assistant, who noticed positron tracks in the cloud chamber after removal of the radiation source. Repeating the experiment, positron tracks were observed to persist and decrease with a half-life of approximately three and one-half minutes. Replacing the aluminum with boron again resulted in persisting positron tracks but with a fourteen-minute half-life. Marie Curie was called to witness her son-in-law's defeat of phosphorus-30 from the aluminum target. "Joliot remembered with pride and affection the expression of intense joy that came over Marie's face when she held the first artificial radioactive element to the Geiger counter, to hear the crackling of the rate meter."\textsuperscript{28} Irène and Frédéric reported in Nature, 10 February 1934, "...when an aluminum foil is irradiated on a polonium preparation, the emission of positrons does not cease immediately when the active preparation is removed. The foil remains radioactive and the emission decays exponentially...We propose for the new radio-elements...the names radionitrogen, radiosilicon, radiophosphorus. These elements and similar ones may possibly be formed with other bombarding particles; protons, deuterons, neutrons..." They sent telegrams to laboratories that could confirm or deny. Using accelerated deuterons (deuterons), E. O. Lawrence at UCB on 27 February 1934 and C. C. Lauritsen at CIT on 1 March 1934 both confirmed the Joliot-Curie report.\textsuperscript{29}

For Enrico Fermi at the Royal University in Rome, an accelerator was unobtainable. He reasoned that since uncharged neutrons did not require high energies to surmount the Coulomb barrier and enter the nucleus, by using neutrons he should be able to test, not only the Joliot-Curie's transmutation of light elements, but also the penetration and transmutation of the heavier elements as well. Fermi's source of neutrons (which he had devised in 1932 promptly after Chadwick's discovery of the neutron) were glass tubes filled with beryllium and 800 mCi of radon obtained from the radium-radon cows used for radiotherapy. After reading the 10 February Joliot-Curie's report, he obtained a number of elements and made them into cylinders that surrounded his neu-
tron-emitting test tubes. After removal of the neutron source, Geiger-Müller tubes were inserted to measure the elements' radioactivities. On 10 April 1934 Fermi sent a letter to Nature confirming the 10 February report of Joliot-Curie by finding that aluminum, silicon, phosphorus, and the heavier elements, chromium, silver, and iodine, all became intensely radioactive after neutron bombardment. These were the corresponding heavier radioisotopes that decayed by beta emission, not new elements with positron emission that the Joliot-Curies had produced by alpha bombardment. Fermi subsequently observed that light elements slowed fast neutrons through multiple nonpenetrating collisions. These slow neutrons produced more target radioactivity, because they spent more time close to target nuclei, increasing the probability of entry and transmutation. Fermi called the measurable probability of capture of neutrons with specified energy the "capture cross section" (Fig. 18.8). He continued his survey of the elements bombarded by neutrons to include uranium. His publication of 15 July 1934 stated that since all the other elements yielded heavier isotopes, either uranium also yielded a heavier isotope of uranium or, if the chemistry was not consistent, it must be the first transuranic element.

Shortly after in the same year, Ida Noddack, a German chemist, disagreed. Her chemical analysis of the target after neutron bombardment of uranium showed the presence of lighter elements. The nucleus must have broken apart.

This was confirmed by O. Hahn (1879–1968) in his 1939 fission article and explained in the same year by L. Meitner's (1878–1968) theory of fission. After more than a hundred quick confirmations there was sudden silence, followed by Einstein's secret letter to President Roosevelt in 1939. Fermi had already described the moderators necessary for chain reaction: heavy water, helium, beryllium, and carbon. In 1938 Fermi left Italy with his family to receive the Nobel Prize, never to return. On 2 December 1942 Fermi started up the first nuclear reactor in Chicago under the secret Manhattan Engineering District plan. The Oak Ridge reactor went critical eleven months later. The Manhattan Engineering District kept nuclear science secret until 1947; by that point, its reactors could make radioisotopes in Curie amounts.

THE DEVELOPMENT OF NUCLEAR MEDICINE: 1930–1945

The application of isotopes to human metabolism in health and disease began with Harold Urey's (1893–1981) gift to his friend Hevesy of a sample of heavy water shortly after his discovery of the stable hydrogen isotope deuterium in 1932. Hevesy promptly began tracer studies of body composition and metabolism by applying his indicator method and in 1933 determined total volume and turnover of body water in fish as well as in himself. The next year, after the production of artificial radioisotopes by Joliot-Curie using alpha bombardment and by Fermi with neutron bombardment, Hevesy produced his own radioisotopes by bombarding sulfur with neutrons as described by Fermi. Phosphorus-32 (32P) was highly suitable for tracer metabolic studies because of its easily detected energetic beta emission, convenient half life of fourteen days, and biological importance in liv-
Fig. 18.9 Sweden issued this postage stamp to commemorate Hevesy’s 1943 Nobel Prize in chemistry. The stamp shows the autoradiograph of a radioactive tracer inside a living cell. (Courtesy of Chuck Mitchell)

Fig. 18.10 Robley Evans (1907–1995). (Courtesy of the Center for the American History of Radiology, Reston, Va.)

Fig. 18.11 John H. Lawrence (1904–1991). (Courtesy of the Center for the American History of Radiology, Reston, Va.)

ing organisms. His 1935 report of $^{32}$P experiments with rats concluded, “The results strongly support the view that the formation of the bones is a dynamic process, the bones continuously taking up phosphorus atoms which are partly or wholly lost again and are replaced by other phosphorus atoms.” This sweeping statement sharply contradicted the traditional view of static completion of bone growth. During the next five years Hevesy invented neutron activation analysis to facilitate his studies of the rare earth elements (associated with his discovery of hafnium) and developed his $^{32}$P studies to include all of the following: plant metabolism, animal bone metabolism, the metabolic turnover of DNA in the spleen and intestinal mucosa of the rat, membrane permeability of cells and frog skin, and blood volume measurements with $^{32}$P labeled red cells. Hevesy’s pioneering studies awakened biologists and physicians to the radioisotopic tracer key that could unlock the door to the invisible world of the kinetics of metabolism. Hevesy was awarded the 1943 Nobel Prize in chemistry and gave his recipient lecture on “Isotope Indicators” (Fig. 18.9).

Robley Evans, a physicist at the Massachusetts Institute of Technology (MIT), in 1936 produced iodine-128 ($^{128}$I) by neutron bombardment as described by Fermi for the study of thyroid metabolism (Fig. 18.10). This study was begun the following year when S. Hertz injected rabbits with the $^{128}$I produced by Evans. Joseph Hamilton (1907–1957) at UCB was interested in human thyroid metabolism and visited Hertz and Evans in Boston. Upon his return, frustrated by the disproportionately short twenty-eight-minute half life of $^{128}$I, he asked Glen Seaborg whether he could produce a radioiodine with a half life of about one week. A few weeks later in 1938, Seaborg and J. Livingood, using the cyclotron of the Lawrence Radiation Laboratory, filled his prescription when they created iodine-131 ($^{131}$I) with its eight-day half life. Hamilton was now able to study iodine metabolism in normal humans and, with M. Soley in 1939, measured human $^{131}$I thyroid uptake with a Geiger tube.
During this period John H. Lawrence (Fig. 18.11) at Donner Laboratory UCB, the biomedical division of his brother E. O.'s radiation laboratory, focused on the therapeutic potential of $^{32}$P, a beta emitter with high energy that localized in bone. After studies of normal, leukemic, and lymphomatous animals in 1937, he pioneered radioisotopic therapy with internally administered unsealed sources. Using $^{32}$P, Lawrence successfully treated his first patient, a young man with chronic myelocytic leukemia. In 1939 he also used $^{32}$P successfully for the treatment of chronic lymphatic leukemia and palpocytopenia vera. That $^{32}$P would be the treatment of choice for these hematologic disorders of excess bone marrow production of white and red blood cells was confirmed in 1941 and in subsequent articles by the hematologist E. Osgood at the University of Oregon School of Medicine. The investigation of hematologic disorders of red cell production and destruction and iron metabolism began in 1937 with the studies of Paul Hahn, a graduate student in the department of pathology, University of Rochester, under George Whipple, Whipple, after leaving UCB for Rochester, had asked Seaborg at the Lawrence Radiation Laboratory to produce a reasonably long-lived radioiron for his hemoglobin studies of anemia. Soon after, Seaborg and Livingood produced forty-five-day iron-$^{59}$ ($^{59}$Fe), the first radioisotope to fill a doctor's prescription; $^{59}$Fe was the second $^{55}$ Measurement of red cell volume and plasma volume is essential for determinations of red cell production, destruction, and turnover. Using $^{55}$Fe produced in Berkeley by deuterium bombardment of iron, Hahn was able to measure accurately total body red cell volume in dogs. However, the total body plasma volume calculated by using the leg vein hematocrit, the ratio of red cell volume to blood volume, was considerably smaller than the actual plasma volume. In 1942 Hahn and M. Chapin independently demonstrated that the body hematocrit was variably smaller than the large vessel hematocrit because of the markedly decreased hematocrit of blood in the small capillary vessels. The previous year J. E. Ross, also in Whipple's laboratory, reported that iron absorption was increased in individuals with iron deficiency anemia. C. Moore in 1944 made the important finding that ferrous iron was much better absorbed than ferric iron.

The successful treatment of hyperthyroidism with $^{131}$I was begun by J. Hamilton in 1941. That same year the third therapeutic radioisotope was administered, also at Donner Laboratory UCB. Charles Pecher (1912-1941), a Belgian postdoctoral fellow, had found in 1940 that after injection of fifty-five-day pure beta emitter strontium-$^{89}$ ($^{89}$Sr) into mice and rabbits, maximum localization in bone occurred within a few hours. The next year, under J. H. Lawrence's supervision, patients with metastatic prostate cancer in bone were treated successfully with 8 mCi $^{89}$Sr. Pecher's only article on $^{89}$Sr therapy was hastily written and submitted just before his forced recall to military duty in Belgium and his untimely death. The article was completed by the editor and published posthumously. Fifty years later, after confirmation of Pecher's findings and the availability of $^{89}$Sr, it has become widely used as the treatment of choice for the palliation of metastases to bone.
A fortuitous meeting in 1943 extended the successful \(^{131}\)I therapy of hyperthyroidism to thyroid cancer and markedly accelerated the development of nuclear medicine. Samuel Seidlin, an endocrinologist, examined a remarkable hyperthyroid patient with severe bone pain whose thyroid had been completely removed surgically twenty years earlier because of thyroid carcinoma. Geiger counter measurements revealed active uptake of radiiodine in numerous bone metastases of the skull, rib, pelvis, and leg, but no uptake in the neck (Fig. 18.12). After fractional administration of 158 mCi \(^{131}\)I during twenty-one months, the hyperactive metastases were destroyed so that the patient was free of pain, gained weight, and felt well. Seidlin’s report in the Journal of the American Medical Association, 7 December 1946, occurred during a congressional debate on atomic controls and generated nationwide newspaper reports of the cure of cancer by radioactive iodine. Marshall Bruce (1913–1994), the first chairman of the Medical Division of the Oak Ridge Institute of Nuclear Studies, commented on the fallout from the Seidlin report, “…a remarkable transposition occurred in the newspapers: ‘CANCER CURE FOUND IN THE FIERY CANYONS OF DEATH AT OAK RIDGE.’ Within days every congressman heard from his constituency. Within hours the brand new Atomic Energy Commission (AEC) commissioners knew they now had two jobs: to stockpile bombs behind closed doors and to pour money into cancer research out in the open. During the next ten years, nuclear medicine was nurtured on the strength of the Seidlin article.”

**The Blossoming and Efficacy of Nuclear Medicine: 1946–1994**

**Instrumentation**

Most of the medically useful isotopes can be produced by neutron bombardment. After the atomic blasts in 1945 ended World War II and the associated secrecy concerning the existence of reactors, many radionuclides became available from the Oak Ridge reactor. Annual shipments to United States medical facilities of more than 50 radionuclides grew from 94 in 1947 to more than the 8,100 shipped in 1954 for just these radionuclides: 5,000 \(^{131}\)I, 2,500 \(^{32}\)P, and 622 gold-198 (\(^{198}\)Au). In 1946 the Geiger counter, far more useful than the gold-leaf electroscope of Rutherford, Hevesy, and the Curies, was the best instrument for clinical measurements. It was used to measure thyroid uptake and to manually survey the body for foci of radioactivity, as Seidlin demonstrated to such great effect. The Geiger counter was indispensable for measurement of samples, administered doses, and point body counting. Though quite sensitive for alpha and beta particles, it detected gamma rays inefficiently, with a sensitivity for \(^{131}\)I of less than 1 percent. In 1947, just when inexpensive radionuclides produced by the Oak Ridge reactor were becoming widely distributed, a German physics professor in Berlin demonstrated a far more efficient detector that became the essential component of all major nuclear medicine instrumentation developed during the next fifty years. Hartmut Kallman had remembered that Rutherford counted alpha particles by the light flashes they produced when striking zinc sulfide screens. Within the American sector of Berlin, Kallman extended to electrons and gamma rays his pre-World War II innovative research of neutron fluorescent photography. Using electron photomultiplier tubes and naphthalene crystals he had formed from mothballs, his new detector counted both the number and the intensity proportional to energy of the scintillations produced by gamma rays as well as by alpha and beta particles. The following year R. Hofstadter improved the scintillation detector by inventing the more efficient gamma ray scintillation crystal, thallium-activated sodium iodide.

In 1950 Hal Anger devised the well counter using anthracene crystals arranged around a well to assay radioactive samples contained in small glass
The anthracene crystal was soon replaced by a sodium iodide scintillation crystal with a hole drilled in the center. The first rectilinear scintillation scanner was constructed by Benedict Cassen and demonstrated in 1950 (Fig. 18.13). This scanner was subsequently improved by substituting sodium iodide for the calcium tungstate crystal, substituting for the pen or arc marker on paper the filmed glow lamp intensity modulated by the count rate devised by David Kuhl in 1952, and replacing the single hole collimator with the multichannel focused collimator developed by Robert Newell and associates in the same year. This instrument produced excellent high contrast photoscans that were the standard of clinical nuclear medicine practice until the 1970s. The first whole body scanner was constructed by Hal Anger in 1951 using ten scintillation detector counters that produced a twenty-line image by scanning across the patient's body, then indexing half the distance between the counters and scanning in the reverse direction. Adjacent areas were then scanned by indexing the patient's table and repeating the operation until the entire body was scanned (Fig. 18.14a). The Mark II improvement of this whole body scanner produced a head-to-toe scan of a patient in a six to twenty-two minute traverse of a moving table over a bank of sixty-four scintillation counters, each with 1.5-inch-thick sodium iodide crystals (Fig. 18.14b). At the same time, 60 keV gamma rays directed from an americium-241 source above the patient produced an additional transmission outline image of the body superimposed over the emission scan.

Hal Anger made a preliminary version of the gamma camera in 1952 that used a pinhole collimator and a flat sodium iodide crystal with a sensitive sheet of photographic film in contact. Sensitivity was not sufficient for clinical use. Then in 1956, by loosely coupling seven photomultiplier tubes to a 4-inch diameter by 1/4-inch thick sodium iodide crystal and combining the seven output signals, the position and energy of each scintillation was obtained as follows. First, the outputs were added to give an energy signal which was sent to a pulse-height selector which rejected the lower-energy scattered gamma rays. Then the signals from the phototubes on the left were subtracted from those on the right, giving the position of the scintillation in the right-left direction. A similar operation gave the position in the orthogonal direction. Then both signals were used to direct the beam of a cathode-ray tube to the position of the scintillation, and the beam was turned on momentarily producing a point flash of light. A photographic camera viewed the cathode-ray tube screen, and the developed film showed an integrated image of the distributed radioactivity. The Anger scintillation camera made it possible to detect and record simultaneously the temporal sequence of the spatial distribution of radioactivity in all areas of the body during any increments of time. Subsequent development of the Anger camera during the next two decades with the use of large crystals, multichannel parallel hole collimators, maceuticals revolutionized clinical nuclear medicine. Six-hour half-life $^{99m}$Tc and
its parent sixty-five-hour molybdenum-99 (99Mo) were discovered by E. Segré in 1938. In particular, the single emission of 140 keV gamma rays with a six-hour half life by 99mTc is ideally suited for the gamma camera. It permits the use of thin crystals with good spatial resolution and sensitivity and the administration of multimicroliter doses to obtain good images in small time increments for rapid kinetic studies of function. An era of labeling radiopharmaceuticals with 99mTc was initiated by G. Subramanian in 1969. Before computerization of the camera in the late 1970s, these studies were performed by manually pulling Polaroid films at rates up to one per second. Subsequent use of electronic formatters, dedicated computer systems, and physiologic gating improved image quality and increased the rate at which images could be acquired for the quantitative measurement of kinetic function of the heart and other organs. The widespread use of compact powerful computers with sophisticated software was made possible by Shockley's manufacture of integrated circuit chips in 1955.

Hal Anger combined the camera with focused collimator rectilinear scanning in 1965 to construct the longitudinal multiplane tomographic scanner, the first instrument to produce multiple images focused at different depths from a single scan of a patient. One scan of a recumbent patient with dual opposed focused collimators could produce twelve coronal planes in which the images were sharp for the radioactivity present in those planes. For each image, activity on or near the designated plane was sharply focused, while activities on the other planes were blurred. The optical-mechanical readout system on the prototype model was subsequently replaced by a computer system in the commercial version that stored and displayed the images and analyzed for numerical data. Hal Anger developed an eighty-lens camera for fast frame perfusion in 1976 that also was later replaced by a computer system.

In 1964 Kuhl and Edwards initiated the development of transaxial single photon emission computerized tomography (SPECT) with uncompensated transverse section imaging using a pair of opposed collimated detectors (SPET) (Fig. 18.15). A series of tangential transverse scans around the patient were generated in angular increments of 15 degrees. The back
projection of each scan was displayed on a cathode-ray tube and all projections were integrated on film. Data were acquired a few years later by rotating the patient in 45-degree increments in front of a stationary Anger camera. In 1975 Kuhl added computerized scanning to transaxial tomography. The prototype of current SPECT cameras was constructed in 1977 by Jaszczak. The widespread use of SPECT a decade later resulted from rapid improvements in computerization, software, gantry design, and technical developments of the Anger scintillation camera. Data are currently reconstructed and reformatted by complex algorithms to provide body transaxial, coronal, and sagittal slices and in addition, to furnish these slices along any axis desired, such as the long axis of the heart. SPECT has become indispensable, especially for clinical imaging of the heart, brain, spine, and joints.

Gordon Brownell initiated the development of positron emission scanning using dual detectors in 1953 (Fig. 18.16).66 Emitted positrons immediately collide with an electron, and both are annihilated producing two 511 keV gamma rays that travel in diametrically opposite directions. Localization of the positron emitter is based upon the selection of the consequent pairs of coincidental scintillations that occur in the opposing detectors around the patient. These radionuclides are important because for elements such as carbon, nitrogen, oxygen, and fluoride, which can be used to label active
biologic compounds, there are no single-gamma ray emitting isotopes that have a suitable half life and emitting energy. Hal Anger used an opposing scintillation camera in 1959 to localize topographically the distribution of positron-emitting radionuclides. The system could electronically select various planes with sharply focused activity located on or near the selected plane while other activity was blurred. Focal plane tomography was developed by Burkham and Brownell in 1972 using a dual-headed multidetector camera. Limited data sampling and the lack of computed tomography (CT) produced suboptimal images. Using a hexagonal ring of twenty-four scintillation counters, Ter Pogossian and associates developed the first computerized positron emission transaxial tomographic scanner (PETT, later PET) in 1974. Subsequent rapid improvements led to the current PET systems that commonly use circular rings of numerous small scintillation block detectors that can obtain spatial resolution of 4 to 6 millimeters. Positron emitters are cyclotron-produced. Their short half lives have required the close proximity of cyclotrons and PET cameras. During this long period of development, research hospitals, institutes, and laboratories with PET cameras have necessarily used their own large cyclotrons. Associated radiochemistry laboratories were also needed for rapid synthesis of positron emitting biochemicals with half lives as short as two minutes. Currently, miniaturized cyclotrons, simplified operations, and automated chemical synthesis for routine production of labeled compounds are all integrated into PET technology.

Radiopharmaceuticals and Procedures in Clinical Research and Practice

Blood

Blood measurements of red cell volume performed in 1942 by Hahn and Chapin with $^{59}$Fe-red blood cells ($^{59}$Fe-RBC) were facilitated by the use of $^{32}$P-RBC by Hevesy in the same year and two years later by G. Nylin. Based upon the earlier work of J. Fine in 1942 in labeling of plasma albumin with $^{131}$I, $^{131}$I-human serum albumin (RISA or $^{131}$I-HSA) was used to measure plasma volume by J. Storaasli in 1949. Blood volume could now be determined accurately in clinical practice by independent measurements of both red cell volume and plasma volume. The next year S. Gray and K. Sterling measured red cell volume with chromium-51-RBC ($^{51}$Cr-RBC). Since $^{51}$Cr elution from red cells is much slower than that of $^{32}$P, $^{51}$Cr-RBC was used in 1953 to determine red cell survival in the clinic by G. LeRoy and in blood storage by F. Ebaugh. It was also used by R. Schilling in 1955 to determine the degree of splenic red cell sequestration by point counting over the

![Fig. 18.17 The Donner Laboratory (Berkeley) automated counter recorded five scintillation point probes simultaneously. Known as "the Monster," the counter was designed and built in 1952 for the study of human kinetics using the 1.1 and 1.3 MeV gamma rays of $^{9}$Fe. (Author's collection)]
spleen, liver, and heart.\textsuperscript{74,75} Using the fixed label \textsuperscript{32}P, the red cell regeneration rate was measured by D. Grob in 1947, and the life spans of red cells, white cells, and platelets were determined by J. Cohen in 1954 and A. Mauer in 1960.\textsuperscript{76,77,78} Red blood cell iron utilization and turnover plasma iron clearance and its localization by point counting were determined using \textsuperscript{59}Fe.\textsuperscript{79,80,81,82} Iron kinetic studies with plasma, red cell, and external point counting of \textsuperscript{59}Fe clarified the physiology in normal subjects and pathophysiology of patients with anemias and iron overload by quantifying hemoglobin synthesis, red cell lifespan, and storage iron deposition and by locating the sites and rates of red cell production and destruction (Fig. 18.17).\textsuperscript{83,84} Good images of \textsuperscript{52}Fe distribution in the bone marrow of normal subjects and patients with hematologic disorders were obtained using the Anger positron camera.\textsuperscript{85} Continuous measurement of breath \textsuperscript{14}CO\textsubscript{2} specific activity after intravenous administration of \textsuperscript{14}C-histidine to normal subjects and patients with megaloblastic anemia differentiated between the metabolic abnormalities of vitamin B\textsubscript{12} deficiency and folic acid deficiency.\textsuperscript{86} The labeling of white blood cells and platelets in saline with indium-111 (\textsuperscript{111}In) using oxine made possible imaging of their concentration at sites of infection and thrombosis, respectively.\textsuperscript{87,88,89} Subsequent \textsuperscript{111}In labeling of white blood cells and platelets in plasma using tropolone was more physiological, permitting immediate cellular function after injection without artificial pulmonary sequestration of cells traumatized by suspension in saline.\textsuperscript{90} The specificity of \textsuperscript{111}In granulocytes for the localization of pyogenic infection has decreased the use of nonspecific gallium-67 (\textsuperscript{67}Ga) for this purpose. For more than two decades, in addition to tumor detection, \textsuperscript{67}Ga has been efficacious in detecting sites of infection and inflammation and remains the agent of choice in the detection and evaluation of pneumocystis carinii lung infection of acquired immune deficiency syndrome patients.\textsuperscript{91,92,93,94}

Gastrointestine

The measurements of iron absorption in humans using \textsuperscript{59}Fe, initiated by P. Hahn and J. Ross and continued by C. Moore during World War II, were refined by them and others using labeled food iron as well as inorganic iron in normal subjects and patients with hematologic and other clinical disorders. Using gamma spectrometry and whole-body counting, body iron loss as well as absorption was determined accurately.\textsuperscript{95,96} Intestinal iron absorption studies were performed using \textsuperscript{52}Fe and the Anger positron camera.\textsuperscript{97} After vitamin B\textsubscript{12} was crystallized by T. Woud in 1947, it was labeled with cobalt-60 (\textsuperscript{60}Co) by Rosenblum in 1950.\textsuperscript{98,99} The adequacy of intrinsic factor secretion was subsequently readily assessed by measuring \textsuperscript{60}Co in a twenty-four-hour urine collection obtained after ingestion of [\textsuperscript{60}Co]vitamin B\textsubscript{12} without and, if indicated, once again with intrinsic factor followed by a flushing dose of unlabeled vitamin B\textsubscript{12}.\textsuperscript{100} Direct measurements of vitamin B\textsubscript{12} absorption were subsequently developed using stool collection, whole body counting, and repeated point counting of the liver after ingestion and injection of [\textsuperscript{60}Co]vitamin B\textsubscript{12}. However, none of these methods is as simple and convenient as the Schilling test, especially after the introduction of the test with simultaneous ingestion of both free [\textsuperscript{57}Co]vitamin B\textsubscript{12} and bound [\textsuperscript{55}Co]vitamin B\textsubscript{12}-intrinsic factor and the test's subsequent commercial availability.\textsuperscript{101} Gastrointestinal bleeding was first measured with in vitro labeled \textsuperscript{51}Cr-RBC by J. Halsted in 1956, then with in vivo labeled \textsuperscript{59}Fe by Pollycove in 1957.\textsuperscript{102,103} The site of bleeding was first localized with the Anger camera using \textsuperscript{99m}Tc-HSA and soon after with the current procedure of choice, \textsuperscript{99m}Tc-RBC.\textsuperscript{104,105,106,107} Studies of gastrointestinal motility were initiated by serial imaging of the stomach after ingestion of radioactive meals.\textsuperscript{108} This procedure was simplified by mixing \textsuperscript{99m}Tc-SC with food.\textsuperscript{109,110} Scintigraphic evaluation of gastric emptying is quanti-
fied accurately by using the sequential geometric means of anterior and posterior images of gastric radioactivity. 111 Gastroesophageal reflux of ingested orange juice after incremental abdominal pressure and esophageal transit time of swallowed liquid or food were measured using mixed 99mTc-SC. 112, 113, 114 Duodenogastric reflux is measured using both intravenously injected 99mTc-iminodiacetic acid for cholecintigraphy and ingested 111In in mixed in a fatty meal to delineate the stomach. 115 Ectopic gastric mucosa in a Meckel's diverticulum concentrates 99mTc-pertechnetate (99mTcO4−) paralleling gastric uptake and persistence. 116, 117 Abnormal bacterial deconjugation, malabsorption of bile salts, and intestinal transit time are determined by sequential abdominal scintigraphic imaging and measured collections of expired 14CO2 after the simultaneous ingestion of both [14C] glycine cholate and 99mTc-SC. 118, 119

Thyroid

The initial 131I thyroid uptake measurements made with Geiger tubes became widely used a decade later, but with inaccurate results (Fig. 18.18). 120, 121 Analysis of a worldwide thyroid uptake survey, using manikins with calibrated thyroid long-lived mock 151I, disclosed the sources of error to be neglect of body background and secondary gamma ray scatter from the neck that required measuring the 100 percent standard in a neck phantom mimicking neck scatter (Fig. 18.19). 122 With replacement of the Geiger tube by the standardized use of scintillation probe spectrometry for thyroid uptake measurement, the measurements of 131I uptake became reasonably accurate and largely replaced the diagnostic use of basal metabolic rate in thyroid disorders (Figs. 18.20a and 18.20b). 123 Routine use of 131I images for screening the thyroid was gradually replaced by 99mTcO4− (initially used by Paul Harper in 1962) during the 1970s and 1980s. 124 Though 123I has a desirable thirteen-hour half life and emits 159 keV gamma rays without beta particles, almost twenty years passed between the cyclotron production of 123I from antimony-121 (121Sb) by Marquez in 1949 and its initial clinical use by H. Wagner in 1967. 125, 126 Though now used widely for thyroid imaging, the high cost of producing contaminant free 123I remains a significant consideration. Multimillicurie doses of 131I are used in treatment of hyperthyroidism and in whole body

Fig. 18.19 Marshall Brucker (1913–1994) with the Oak Ridge set of anthropomorphic phantoms that was circulated to several hundred laboratories in an effort to obtain standardization of measurement of thyroid uptake. The thyroids were filled with different amounts of "mock iodine," a mixture of long-lived radionuclides with characteristics similar to 131I. (Author’s collection)
ventricular blood pool activity enabled assessment of regional wall motion both at rest and with exercise. Comparison of diastolic and systolic left ventricular radioactivity permitted the calculation of ejection fraction and its measurement with $^{99m}$Tc-HSA. Right ventricular ejection fraction was assessed by analysis of first pass right ventricular radioactivity. Ejection fractions were also measured using a portable precordial probe detector.

Myocardial uptake of the bone agent $^{99m}$Tc-Sn-pyrophosphate developed by Mallinckrodt in 1973 was demonstrated during the first week of infarction. After introduction of the potassium analogue thallium-201 ($^{201}$TI) as a myocardial perfusion agent by Lebowitz in 1973, $^{201}$TI perfusion and redistribution were assessed both at rest and with maximal exercise, or equivalent dipyridamole injection to detect regions of myocardial ischemia and infarction. The sensitivity and accuracy of regional detection and localization of perfusion defects were increased markedly by the gradual replacement of planar imaging by SPECT during the eighties. The AEC was terminated in 1975 and its responsibilities divided between the Nuclear Regulatory Commission and the Department of Energy (ERDA). After twenty years of safe rapid introduction of new radiopharmaceuticals under AEC control, the Food and Drug Administration (FDA) terminated its exemption of radiopharmaceuticals in 1975. New tracer radiopharmaceuticals became subject to the same lengthy review process for safety and efficacy that the FDA used for active pharmacologic agents. Fifteen years later, and six years after the first $^{99m}$Tc-isonitrile was used successfully to image myocardial perfusion, the FDA finally approved two new isonitrile myocardial perfusion agents, $^{99m}$Tc-sestamibi and $^{99m}$Tc-

**Heart**

Twenty-five years after H. Blumgart measured circulation times in humans with radon, precordial Geiger tube probe counting with $^{131}$I-HSA was used to record radiocardiograms in humans and measure cardiac output in dogs. Using the same technique with scintillation detector probes in humans together with arterial blood sampling, comparison of the two cardiac outputs measured simultaneously demonstrated that the results of the radiocardiogram and Fick methods were in close agreement. Static rectilinear scanning of the cardiac blood pool with $^{131}$I-HSA was supplanted by images obtained with the Anger scintillation camera, initially using rapid sequential Polaroid frames, and subsequently with ECG gating of computerized acquisition. Gating of left imaging for detection, location, and subsequent treatment of metastatic thyroid carcinoma.

**Fig. 18.20a** Herbert C. Allen, Jr., manually scans the thyroid through plexiglass plate bearing square coordinates, ca. 1950. (Courtesy of the Center for the American History of Radiology, Reston, Va.; from the E. R. N. Grigg Collection)

**Fig. 18.20b** The resulting scans provided new challenges to diagnostic interpretation. (Courtesy of the Center for the American History of Radiology, Reston, Va.; from the E. R. N. Grigg Collection)
teboroxime, that replace with the desirable properties of $^{99m}$Tc the limiting low gamma ray energy (68–83 keV) and relatively long half life (seventy-three hours) of $^{201}$TI.\textsuperscript{14,16}

The current use of PET with cyclotron produced $[^{18}$F]fluorodeoxyglucose provides the best evaluation of regional myocardial metabolism in addition to assessing myocardial perfusion with $[^{1}$H]ammonia or generator produced rubidium-82 ($^{82}$Rb).\textsuperscript{14,145}

**Bone**

Twenty years after C. Pecher's posthumously published article on the rapid localization in bone of the pure beta emitter $^{89}$Sr in mice and rabbits, the first bone scans performed with $^{89}$Sr were followed by scans with $^{87}$Sr.\textsuperscript{145,146} $^{99m}$Tc labeled bone agents were introduced in 1972 with polyphosphate and several diphosphonates.\textsuperscript{147} The bone agent of choice, $^{99m}$Tc-Sn-methylene diphosphonate ($^{99m}$Tc-MDP), was introduced three years later.\textsuperscript{148} The sensitivity of the bone scan in early detection of many bone disorders, including inflammatory, infectious, and especially malignant primary and metastatic lesions, rapidly led to its frequent use. The effective $^{89}$Sr palliation of metastatic cancer bone pain reported by J. Lawrence and C. Pecher in 1942 was successfully brought back for the therapy of metastatic prostate and breast cancer.\textsuperscript{140,150,151}

**Liver**

The demonstration in 1944 by E. Dobson and H. Jones that the clearance rate of $^{51}$CrPO$_4$ colloid is a function of particle size formed the basis of liver/spleen imaging and blood flow procedures utilizing reticuloendothelial cell phagocytosis of colloidal particles.\textsuperscript{152} Dobson next used $^{32}$P colloid and $^{51}$CrPO$_4$ colloid to measure liver blood flow.\textsuperscript{152,154} The use of $^{198}$Au colloid and $^{131}$I-macroaggregated albumin ($^{131}$I-MAA) for liver/spleen imaging was replaced in the 1960s by the current agent of choice, $^{99m}$Tc-sulfur colloid.\textsuperscript{153,156,157,158,159,160,161} Cholescintigraphy for hepatobiliary function began with $^{131}$I-Rose Bengal and was replaced in the 1970s by $^{99m}$Tc-iminodiacetic acid (currently $^{99m}$Tc-DISIDA) and, if indicated, with intravenous morphine to facilitate gall bladder filling or cholecystokinin to stimulate gall bladder contraction.\textsuperscript{162,165,164,165}

**Kidney**

The initial renogram assessment of renal function by external probe point counting of the kidneys used both $^{131}$I-hippururate and $^{131}$I-diodrast.\textsuperscript{166} While the latter was quickly abandoned, the $^{131}$I-hippurate renogram has for almost forty years continued to provide valuable diagnostic information on renal perfusion, glomerular filtration, tubular extraction, and renal excretion. The renal clearance of $^{131}$I-hippurate is similar to that of para-aminohippuric acid, which is normally cleared completely in a single pass, 20 percent by the glomeruli and 80 percent by the tubules.\textsuperscript{167} Rectangular collimators were devised for point counting of the kidneys, and mercury-203 ($^{203}$Hg) chlormerodrin was introduced to provide fixed uptake suitable for rectilinear scanning.\textsuperscript{168} At this time the vesicoureteral reflux test was introduced but not applied clinically until the later use of the Anger camera with $^{99m}$TeO$_4$.\textsuperscript{169,170} The use of the camera for $^{131}$I-hippuran renography began with sequential Polaroid snapshots and after computerization in the 1970s was developed into quantitative region of interest (ROI) analyses.\textsuperscript{171,172,173} After the transient use of $^{99m}$Tc-Sn-gluconate and $^{99m}$Tc-EDTA, two very useful currently used radiopharmaceuticals were introduced.\textsuperscript{174,175} $^{99m}$Tc-DTPA (diethylene-triamine-pentacetic acid) is used to measure glomerular filtration rate and $^{99m}$Tc-DMSA (dimercaptosuccinic acid), a compound retained by the cortex, is used to evaluate perfusion and detect cortical lesions.\textsuperscript{176,177,178} Despite the greatly superior radionuclide physical properties of $^{131}$I-hippuran and $^{99m}$Tc-MAG$_3$ (Mercaptoacetyl-Gly) their high cost has prevented widespread replacement of $^{131}$I-hippuran.\textsuperscript{173,189,181} All three agents are used both with and without the angiotensin II suppressor captopril to evaluate renovascular hypertension.\textsuperscript{182}
Lung

Ventilation of the lung was first evaluated with xenon-133 (133Xe) in 1955 by Conn and Knipping and has remained for forty years the most widely used agent for this purpose. Initial point counting with multiple probes was replaced in the 1970s by the computed tomography Anger camera that made possible regional assessment of the first breath, equilibrium, and washout phases of regional ventilation. Lung perfusion with 131I-microspheres was used to diagnose pulmonary embolism and 209Hg-ceramic pellets used to diagnose pulmonary infarcts. G. Taplin achieved control of micro- and macroaggregation of 131I-HSA from 1.5 to MAA from 1961 to 1964 and later demonstrated the safety of MAA in dogs (1963), the advantages of 131I-HSA aerosol in the diagnosis of chronic obstructive pulmonary disease (1966), and introduced 99mTc-HSA MAA (1970). With the use of 131I-MAA scans in humans massive pulmonary embolism was demonstrated. After 133Xe ventilation (V) and 131I-MAA perfusion (Q) were combined, the importance of initial normal 133Xe ventilation of nonperfused regions (i.e., V/Q mismatch) in the diagnosis of pulmonary embolism was established. 133Xe ventilation followed by 99mTc-MAA perfusion was then routinely used to detect pulmonary embolism. After the development of 99mTc-technetium G. Taplin, 1977), these were also used to evaluate ventilation. While there is general agreement on the interpretation of medium and large embolic images as high probabilities of pulmonary emboli, there is a lack of consensus on the image criteria for the important diagnosis of small emboli (indeterminate or low probability of pulmonary emboli) needed for the initiation of prophylactic heparinization. Inclusion of the patient's history and physical findings together with the image findings may be required to achieve this consensus.

Miscellaneous

Numerous procedures have been developed that are less frequently used, and only a few of the more common ones are mentioned in this brief survey. Placental localization by probe area counting of 131I-HSA by A. Weinberg in 1956 was validated by L. Benet in Caesarian section in 1958. 131I-chloroform and 131I is used as a placental test. The use of 99mTc for placental scanning has been replaced by ultrasound. Scrotal scans of 99mTc bolus injection are efficacious in detecting testicular torsion, epididymitis, and other intrascrotal lesions.

Brain

Brain tumor localization was performed initially with Geiger probe detectors after intravenous injection of 131I-HSA and blood flow evaluated with scintillation probes after bolus injection (Fig. 18.21). The use of 99mTc-O4 with bolus injection and the Anger camera greatly increased the sensitivity and resolution of tumor detection and made possible the evaluation of cerebral blood flow, initially performed with sequential one and one-half second Polaroid frames (Fig. 18.22).

Fig. 18.21 Early efforts at brain mapping included the placement of a single-channel probe on each of the marked areas of a patient's head. The radioactive tracer had been injected sixteen hours earlier (ca. 1958). (Courtesy of the Center for the American History of Radiology, Reston, Va: from the E. R. N. Grigg Collection)
lar $^{99m}$TcO$_4$-DTPA and consequent reduction of brain background activity led to its replacement of $^{99m}$TcO$_4$. During this period quantification of cerebral blood flow for research was performed with krypton-85 ($^{85}$Kr) and $^{133}$Xe using the nitrous oxide method of S. Key and C. Schmidt, 1948. After $^{131}$I-myelograms were introduced by subarachnoid injection of $^{131}$I-HSA, cisternography and ventriculography were initiated and developed, and cerebrospinal fluid rhinorrhea detected with the camera. $^{216,217,218,219,220}$ SPECT evaluation of regional cerebral blood flow and function was initiated by the binding of intravenous injected $^{123}$I-idoamphetamine to cerebral neureceptors and is currently performed with $^{99m}$Tc-hexametazime (HMPAO or hexa-methyl-propyleneamine oxime). $^{221,222,223,224}$ Intravenous injection of acetazolamide, a potent cerebrovascular vasodilator, prior to $^{99m}$Tc-HMPAO injection produces relative inhomogeneity of cerebral blood flow from detected intracranial or extracranial stenoses. $^{225}$ Many research studies using PET with perfusion agents, metabolic agents, and receptor agents, initially imaging dopamine receptors, are localizing complex physiological and biochemical processes in response to normal stimuli and in neurological disorders. $^{226}$ Some of these studies are now performed with SPECT, even with positron emitting agents by using high energy collimators for the 511 keV gamma rays.

**Cancer and Tumors**

The beneficial results of $^{32}$P therapy of chronic leukemia and polycythemia vera, for which it remains the treatment of choice, that were begun in 1937 by John H. Lawrence have been well confirmed for more than fifty years. In 1950 colloidial $^{32}$P$_4$ was used for successful palliation of malignant intracavitary effusions. Soon after, colloidial $^{198}$Au was also used for this purpose associated with a scan, and subsequently used for therapy of chronic intraarticular effusions. $^{228}$ $^{229}$ $^{67}$Ga imaging was shown to be sensitive in staging lymphomas, for which it remains the agent of choice. $^{230}$ $^{201}$Tl was used to detect malignant tumors. $^{231,232}$ Parathyroid adenoma localization was performed by subtraction of the matched $^{99m}$Tc thyroid scan from the $^{201}$Tl scan and is being replaced recently by a single procedure using $^{99m}$Tc-sestamibi. $^{233,234}$ Glucose metabolism of the brain is evaluated with $^{[18F]}$fluorodeoxyglucose ($^{[18F]}$FDG) and effectively differentiates between postsurgical changes and the recurrence of residual tumor. $^{235}$ This PET procedure has been performed recently with SPECT high energy collimators and relatively low resolution. The usefulness of $^{131}$I-metaiodobenzylguanidine-norepinephrine ($^{131}$I-MIBG) in diagnosis and therapy of neuroblastoma and other neuroendocrine tumors was demonstrated by Hoechtl in 1986. $^{236}$ The recent successful use of the somatostatin analogue radiopetide $^{[111In-DTPA-D-Phe]}$-octreotide to image neuroendocrine tumors may replace this diagnostic use of $^{131}$I-MIBG. $^{237,238,239}$ Clinical trials are evaluating the role of this radiopetide in other tumors such as lymphoma, colorectal cancer, and in breast carcinoma when combined with $^{99m}$Tc-sestamibi. Clinical trials of $^{99m}$Tc-P587, a newer somatostatin analogue with similar receptor binding characteristics, also appear promising. The recent clinical use of
Radioassay

The finding in diabetic patients of antibodies to insulin by Berson and Yalow in 1956 led to the development of radioimmunoassay (RIA) as an established procedure. Thousands of ligand/antigens could now be measured with accuracy and precision at sensitivities increased by factors ranging from 10^3 to 10^8. Hormones, proteins, antibodies, antigens, and biochemical compounds could now be measured during their physiologic and pathophysiologic cyclic variations and in their response to various stimuli. Radioimmunoassay has revolutionized not only medicine but all of biology, physiology, pharmacology, laboratory medicine, and biomedical research. After Solomon Berson’s death in 1972, Rosalyn Yalow was awarded the 1977 Nobel Prize in medicine (Fig. 18.23).

CONCLUSION

The current in vivo quantifying of biochemistry, cellular, and organ function by computerized imaging was developed by the resourceful application of Hevesy’s radioactive indicator method. The recent development of new perfusion, metabolic, immunologic, and receptor radiopharmaceuticals coupled with good SPECT and PET spatial resolution are rapidly increasing the major role of nuclear medicine in improving the diagnosis and treatment of patients throughout the world.
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