RADIOISOTOPES in Cardiovascular Disease

Edited by

CHARLES K. FRIEDBERG, M.D.

Guest Editor

Solomon Silver, M.D.

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with 21 contributors

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RADIOISOTOPES (SILVER) SECTION 1

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Preface

This volume is composed of a series of articles reprinted from a symposium in recent issues of the journal PROGRESS IN CARDIOVASCULAR DISEASES. It is designed for those who desire the convenience of possessing the articles in bound form and for those who do not subscribe to the journal but have a special interest in the material of this symposium.

Despite the increasing use of radioisotopes in biochemical and physiologic studies of the circulation and in the diagnosis and treatment of cardiovascular disease, physicians have been further removed from firsthand familiarity with these procedures than from most other laboratory technics. This has been due to the specialized knowledge, skill and instrumentation required, and especially to restrictions imposed on the use of radioisotopes because of their potential hazard. The following symposium is intended to present discussions of the possible application of radioisotopes in cardiovascular disease and to provide an insight into the knowledge of cardiovascular hemodynamics obtained from studies with radioisotopes by authorities who have had firsthand experience in the field. Dr. Solomon Silver contributed to the symposium and acted as guest editor.

Experience has taught that apparently complex developments in the laboratory, seemingly far-removed from the bedside, may rapidly intrude themselves into clinical practice. It is often rewarding to become familiar with at least the principles involved in these laboratory developments during their preclinical state; this facilitates a more profound understanding and a more critical knowledge of their indications, value and limitations when they become a part of clinical usage. Many physicians who first learn of new diagnostic or therapeutic technics after they are in clinical use are often unnecessarily impressed by them when they involve unfamiliar mathematical, biophysical or biochemical principles or procedures, and either avoid them or endow them with a diagnostic importance, reliability or specificity which they do not merit. Earlier and more intimate familiarity may breed a more realistic appraisal. The present symposium is designed to contribute to such an objective.

A glossary has served to introduce the symposium for those who have little or no intimate knowledge of pertinent terms or principles in modern physics. A reading of or reference to this glossary may be indicated for those who do not know when 1 rad is equal to 1 rem and under what circumstances they may differ, who are not familiar with the principle of the mass spectrometer, who do not know the type of radiation emitted during the disintegration of tritium, who are confused by the distinctions between nuclide, element and isotope, and especially for those who might guess that a poisson distribution refers to an arrangement of a school of fish.

Radioisotopes have been used to study metabolic pathways, ionic exchange and the degradation of drugs and other materials introduced into the body. They have provided information as to the turnover, method of action and rate of excretion of such important cardiovascular agents as digitalis, organomercurials and angiotensin. By appropriately labeled substrates it has been

shown that cardiac metabolism is geared to energy production and liberation by pathways via the Embden-Myerhof scheme of glycolysis, fatty acid degradation and the citric acid cycle. Studies with isotopes have demonstrated that cell membranes, including those of myocardial fibers, are permeable to sodium, potassium, chloride and water and have led to the concept of specific, active transport systems for these ions in order to explain the maintenance of ion gradients in various cells and tissues. Isotopic investigations have contributed to our knowledge of the role of potassium and sodium ions in cardiac activation, depolarization and contraction. These fields indicate the broad scope of application of isotopes to cardiovascular physiology.

The use of the isotopic tracer technic has extended our information concerning the disappearance of ions from the vascular system. The curves obtained by recording the concentrations in frequent, serial samples of arterial blood after sudden intravenous, intracardiac or intra-arterial injection of a bolus of radioactive material have been used to determine the cardiac output, the blood volume, the circulation time, the central blood volume and other circulatory quantities as well as the space of distribution of various electrolytes. Slope analysis of the early portion of the isotope curves may be used to determine the mean rate of exchange of isotope between vascular and extravascular pools, and in steady states this indicates the outward transport rate or fraction of isotope leaving the circulation per unit time (rate of turnover). Abnormalities in variously obtained time-concentration isotope curves have been used to diagnose and localize cardiovascular abnormalities. Such studies form the major portion of the presentations in this symposium.

Measurement of certain hemodynamic factors, including cardiac output, blood volume and circulation time, have been made by other technics which do not require the use of radioisotopes. In general, radioisotopes provide the advantages of simple and exact measurement for those who have the necessary facilities and skills. In certain types of measurement, particularly those involving external body surface counters, it is possible to make determinations with radioisotopes which avoid the stresses of injection and catheterization imposed by other technics.

Radioisotopes have been found particularly useful both in the detection of cardiac shunts and quantification of their size, as described by Braunwald and associates. The inhalation of Kr^{85} has been advantageous in permitting the detection of small left-to-right shunts which are missed by the oxygen method, and in providing speedier determinations with smaller samples of blood, thus permitting repeated studies. Kr^{85} can be placed in solution and injected into a vein or into the right cardiac chambers, whereupon 95 per cent of the gas leaves the blood during a single passage through the lungs. Determination of the appearance time of Kr^{85} in expired air after its injection into the left side of the heart has been utilized to detect and localize a left-to-right cardiac shunt, and in the presence of an atrial septal defect to disclose associated mitral regurgitation or ventricular septal defect. The method has been used to detect patent ductus arteriosus and other left-to-right shunts from the aorta, especially when there is an associated intracardiac shunt. Braunwald et al. also describe the use of Kr^{85} to characterize right-to-left shunts after

selective injection of the material into the systemic veins, right cardiac chambers and pulmonary artery and recording curves of the Kr^{85} concentration in arterial blood. They describe a method for determining the cardiac output with Kr^{85} within a few minutes after injection without the use of a densitometer or oximeter but requiring either left-heart or right-heart catheterization.

Methods for measuring the intravascular blood volume are described by Schreiber et al., who recommend that independent determinations be made of plasma volume with the aid of albumin-I^{131} or the blue dye of T^{1824} and of red cell volume with Cr^{51} or P^{32}. Previous errors in measured blood volume are attributed to determinations of hematocrit, since the average body hematocrit is about 92 per cent of the peripheral hematocrit determined from venous blood. They also discuss the blood volume in various forms of heart disease, shock and congestive heart failure.

The use of the isotope dilution technic with radioiodinated (I^{131}) human serum albumin to determine the cardiac output and "central" blood volume and to detect valvular regurgitation is discussed by Glick and associates. They describe a method to estimate "true" pulmonary blood volume in man by simultaneous or rapidly successive injections of isotopic indicators into the pulmonary artery and into the left atrium with sampling of blood from a systemic artery. The mean "true" pulmonary volume determined in normal subjects was 300 ml./M2, which is smaller than that previously estimated.

The recording of precordial dilution curves by the method of body surface counters is of special interest for the determination of cardiac output and "central" blood volume, for screening of patients suspected of possessing a left-to-right cardiac shunt, to confirm closure of such a shunt in the early postoperative period, and to determine the ventricular stroke volume and the fraction of end diastolic volume which it constitutes. These external counting technics may prove particularly advantageous because they obviate the need for catheterization and arterial punctures, and can be used in acutely ill patients, e.g., to determine the cardiac output in myocardial infarction. On the other hand, there are serious difficulties with the method of precordial scanning due to possible errors dependent on the placement of the counter, particularly when trying to obtain reproducible or comparative results at different times, and error due to improper collimation which may not limit the primary curve to the chamber under study.

The use of precordial scanning technics may prove of special value in the measurement of the coronary blood flow as described by Sevelius, since it avoids the coronary sinus catheterization required by the presently employed nitrous oxide technic. The precordial scanning method is based on the assumption that following intravenous injection of radioactive material (I^{131} bound to either human serum albumin or to sodium iodohippurate) the precordial flow curve records a third peak after that representing right and left heart flows, and that this third peak represents coronary flow. The coronary curve must be separated from the heart curve and from the curve of recirculation.

The technics of obtaining precordial isotopic curves (radiocardiography—Prinzmetal) have been extended by selective placement of the injected radio-

active material into specific cardiac chambers or great vessels with the aid of a catheter. This is designed to overcome the error due to overlapping of the right and left heart curves in the radiocardiogram by reducing the circulatory path between the site of injection and the chamber to be studied. Kr^{85} injected into the right atrium has been used to study the right heart curve, and I^{131} human serum albumin injected into the pulmonary artery to study the left heart curve. Under the heading of selective quantitative radiocardiography, Donato has described the measurement or calculation of cardiac output, of changes in left and right cardiac output, the ventricular rate of emptying, the end diastolic and residual ventricular volumes and mean pulmonary blood volume.

A critical review of the factors influencing the interpretation of isotopic tracer studies of body water and electrolytes is presented by Threefoot. He discusses the various methods of determination of total body water and extracellular fluid volume by radioisotopes, indicates the difficulties involved and the reported variations in measured volumes and attributes error to lack of homogeneity of tracer or stability of its distribution. Similar critical analysis has been made of the reported studies of the quantity and distribution of sodium, chloride and potassium, and of other electrolytes. It is pointed out that 30 to 50 per cent of body sodium and similarly of chloride is in compartments other than those freely communicating or in equilibrium with the extracellular compartment.

From the practical clinical viewpoint, radioisotopes have been most widely employed in the diagnosis and treatment of thyrocardiac disease. Silver and associates present their experience with a very large series of cases of hyperthyroidism, many with congestive heart failure and angina pectoris, treated with I^{131}. The symposium is concluded with a discussion of the use of radioiodine to control angina pectoris and congestive heart failure in euthyroid patients by Friedell and associates. They indicate the problem involved in the selection of patients and in the management of patients in whom myxedema is induced. On the basis of their experience and the data recorded in the literature this method of treatment in appropriate cases is highly recommended. But there is no widespread agreement among practicing cardiologists as to precise indications or as to the evaluation of the results obtained.

C. K. F.

Contents

PART ONE

Glossary of Nuclear Terms

By SERGEI FEITELBERG

RADIOACTIVE ISOTOPES are becoming a common diagnostic and research tool in cardiology. Some readers, however, may not yet be familiar with nuclear physics as applied in physiology. Although there are adequate textbooks in this field, it appears desirable to offer some basic information so that references to the use of radioactive nuclides will be intelligible to readers who have not had the opportunity to acquaint themselves with this. A systematic introduction, however short, would go beyond the scope of this journal, and it was suggested, therefore, to present the desired information in the form of a concise glossary of the nuclear terms as they occur in this series of articles.

Beta particles. Radioactive nuclides decay by the emission of a variety of radiations. One such radiation is the emission of beta particles of varying energy. Beta particles are electrons originating in the atomic nucleus. Their energy varies within wide limits.

Blank count, also called background counting rate. When the disintegration rate of some radioactive material is observed by a radiation counter, the counter registers, besides the counting rate of the investigated material, the counting rate generally present at the site of observation. This is due to the presence of naturally occurring radioactive materials on the earth and to the cosmic radiation arriving on the earth from the interstellar space. This background has to be subtracted from the counting rate observed with the sample.

C^{14}. A radioactive isotope of carbon which disintegrates with a half life of 5568 years by emitting low energy beta radiation. It is particularly useful in the labelling of organic compounds.

Ca^{45}. A radioactive isotope of calcium which disintegrates with a half life about 160 days by emitting medium energy beta radiation.

Collimation. When it is necessary to determine the location of a radioactive deposit within the body, radiation detectors can be made directional by enclosing them in a thick-walled tube of a material which absorbs radiation (lead, tungsten, etc.). Such a detector is then "collimated" and it will "see" a source of radiation only when it is on the axis of the collimating tube.

Counting rate. The amount of a radioactive material is determined by using a nuclear counter which converts radiation bursts emitted by a disintegrating

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atom into electrical pulses. These pulses are counted during some time interval. Counting rate is the coefficient of the number of pulses observed and elapsed time. A counting rate computer performs this division automatically; a counting rate meter indicates the counting rate and its changes on a scale; a counting rate recorder writes the counting rate on a strip chart.

Cr^{51}. A radioactive isotope of chromium which disintegrates with a half life of 28 days by emitting medium energy gamma radiation.

Decay scheme gives a complete description of the decay of a given radioactive nuclide: what particles are emitted, what their energies are and what the new daughter element is.

Determination of radioactivity. This may have two meanings: (1) Amount of radioactive material in millicuries; this is determined by observing the counting rate with a nuclear counter .(2) Intensity of radiation emitted by a given source (x-ray machine, some quantity of radioactive material, etc.); this is measured in roentgens per hour by suitably designed and calibrated instruments (nuclear counters, ionization chambers).

Disintegration. Process of nuclear decay during which the radioactive nuclide emits its radiation according to the decay scheme and becomes a new element.

Deuterium. A stable isotope of hydrogen with twice the mass of ordinary hydrogen.

Dual channel rectilinear recorder. A recording rate meter which registers simultaneously the counting rate from two radiation detectors and where the pens deflect not on an arc but in straight lines, normal to the paper chart travel.

Energy of nuclear radiation. Energy of radiation emitted during the decay; it is expressed in million electron volts (Mev) $= 1.6 \times 10^{-12}$ ergs. The range of these energies is usually between 0.1 and 3 Mev.

Exponential fall off. Some physical and physiological processes do not change linearly with time but follow a more complicated mathematical law. Radioactive decay and some concentration changes in body metabolites decrease in such a fashion that whenever a given time interval elapses, the remaining activity or concentration is half of that which was present at the beginning of the interval; after a second such interval, again half only will remain, that is, a quarter of what was present two time intervals before. Such interval is a characteristic of the given process and is called "half life." The following table will illustrate the numerical relationship.

Time	Activity or Concentration
at the beginning	A
1 half life later	A/2
2 half lives later	A/4
3 half lives later	A/8
4 half lives later	A/16
n half lives later	$A/2^n$

It can be seen from the table that remaining activity is an exponential function of the number of half lives or of time generally; hence the term, "exponential fall off."

Fission is the splitting up of heavy atoms into smaller fragments, new elements, called fission products. This process is accompanied by the release of radioactivity and heat, and it occurs, for instance, in the chain reaction pile and during the explosion of an atomic bomb.

Gamma photon. The disintegration of some radioactive nuclide is accompanied by the release of gamma radiation, frequently but not always associated with beta radiation. Gamma radiation is electromagnetic radiation like light. The difference is that the wave length is much shorter and that the quanta of gamma radiation carry much more energy than those of light. A quantum of energy is the smallest "packet" of energy which can appear in nature; a quantum of electromagnetic radiation is called a photon.

Gamma ray spectrometry. In a scintillation counter, the intensity (usually voltage) of the electrical pulse occurring after the absorption of a gamma ray is proportional to the energy of the absorbed photon. The distribution of electrical pulses of various intensity can be determined by suitable instruments (pulse light analyzers). This distribution represents also the distribution of gamma ray energies and is therefore equivalent to a gamma ray spectrum. Gamma ray spectrometry is a basic tool in physical research; in biology it permits the simultaneous observation of two or more radioactive materials by measuring their characteristic peaks independent of one another.

Geiger Mueller counters. A gas filled device equipped with insulated electrodes which produces an electrical pulse when it absorbs radiation of sufficient energy. Exposed to a radioactive isotope, a Geiger Mueller counter will produce electrical pulses whenever a burst of energy emitted during the disintegration of an atom reaches it and is absorbed in it. These pulses can be counted by suitable electronic devices. When the energy of atomic radiation is low, for instance in some beta radiation, the enclosure of the Geiger Mueller counter may prevent the entrance of the radiation into the gas inside the counter. To allow even soft beta particles to enter and to be counted, thin windows, usually of mica, are installed in the counters; such counters are called window counters.

Half life. For definition see "exponential fall off." There are three types of half life which are encountered in biology. 1. Physical half life, T_p, the half life of a radioactive material in vitro. 2. Biological half life, T_b, which characterizes the disappearance of some material from the body or an organ, independent of its physical decay if any (i.e., a stable compound may disappear exponentially from the body by excretion). 3. Combined half life, T_c, which is due both to physical and biological decay; $\frac{1}{T_c} = \frac{1}{T_b} + \frac{1}{T_p}$; combined half life is the parameter which usually can be observed in a biological experiment.

Heavy water. Water where ordinary hydrogen is replaced by heavy hydrogen (Deuterium).

Hydrogen isotopes. (1) Ordinary hydrogen of atomic weight 1, (2) Deuterium, hydrogen of atomic weight 2, which is non-radioactive, and (3) Tritium, hydrogen of atomic weight 3, which is radioactive (half life, 12½ years; emits very soft beta radiation of 0.018 Mev.).

I^{131}. A radioactive isotope of iodine which disintegrates with a half life of 8 days by emitting a variety of medium energy gamma photons and beta particles

I^{131} labelled compounds. Chemical compounds in which I^{131} atoms are incorporated, so that they can be measured and observed in the body because of the radiations emitted by radioactvie iodine.

Isotopes. Atoms of the same element may have different atomic weights. Such atoms are called isotopes. The identity of an element is determined by the nuclear charge due to the number of protons. Atomic weight is determined by the number of protons and neutrons in the nucleus. Since the neutron has no charge, more or fewer neutrons in the nucleus will not change the identity of an element, but it will change the atomic weight. The different isotopes of an element differ in the number of neutrons. Too great an excess or deficit of neutrons in a given nucleus makes it unstable; such an isotope is radioactive. When this deficit or excess is moderate, the isotope need not be radioactive, it may be stable. Most elements have several stable and radioactive isotopes.

K^{42}. Radioactive isotope of potassium which disintegrates with a half life of 12½ hours by emitting high energy beta and gamma radiation.

Kr^{85}. A radioactive isotope of krypton which disintegrates with a half life of 10 years by emitting medium energy beta and gamma radiation.

Back scatter. When gamma ray photons impinge on matter, they may pass through without interaction or they may be totally or partially absorbed. When only part of their energy is absorbed, the remaining energy will consist of gamma ray photons of lower energy and these photons will move not only in the direction of the original radiation, but they will be scattered in all directions (side scatter, back scatter).

Mass spectrometer. An instrument to determine the relative concentration of two stable isotopes in a mixture containing both. It operates on the principle that electrically charged ions moving at a relatively high velocity in vacuum are deflected by a magnetic field and that the deflection depends on the particle velocity, the magnetic field and on particle mass. If velocity and magnetic field are held constant, the deflection will depend on mass alone and this will allow the separation of isotopes of different atomic weight.

Millicurie. Unit to measure the quantity of radioactive material based on disintegration rate: one millicurie is present if 37 million atoms disintegrate in the given sample per second.

Mg^{28}. A radioactive isotope of magnesium which disintegrates with a half life of 21 hours by emitting medium energy beta and gamma radiation.

Neutron. A nuclear particle of nearly the same mass as a proton but without an electrical charge. Neutrons and protons are the main building blocks of atomic nuclei.

Neutron bombardment. When matter is exposed to free neutrons, the atoms can incorporate neutrons into their nuclei with relative ease, since they are not repelled electrostatically by the positively charged protons. This capture of neutrons is one of the methods used to produce isotopes.

Nuclide. A term used to refer to a particular element with a given mass. It

is best explained in connection with the related terms "element" and "isotope." For example, hydrogen is an element. Deuterium and tritium are the same element and they are isotopes of each other. Deuterium per se is a nuclide and it is completely described by its charge and mass; it is also an element, namely hydrogen with most of the chemical properties of any other possible hydrogen, and it is an isotope of other nuclides which have the same atomic number but a different mass.

P^{32}. A radioactive isotope of phosphorus which disintegrates with a half life of 14 days by emitting high energy beta radiation.

Photomultiplier. A vacuum tube usually with 10 electrodes which conducts electricity when exposed to light. It is an extremely sensitive device with a very fast response.

Poisson distribution. A statistical law applicable to the random nature of nuclear disintegration. It permits prediction of errors expected in nuclear counting.

Radiation detectors. Devices which absorb nuclear radiations and convert the absorbed energy into other forms which can be observed. Such other observable forms are chemical changes and electrical current. Example of chemical detectors: photographic film. Example of electrical detectors: Geiger Mueller counter.

Rem. A rem corresponds to the dose in tissue which results in biological damage equivalent to that produced by one rad of medium energy x-radiation. The rad is a measure of radiation dose and corresponds to an energy absorption of ionizing radiation of 100 ergs per gram of tissue. For the usual range of beta, gamma and x-radiation energies, 1 rem = 1 rad; for extreme energies and for rare types of radiation, this is not the case. For alpha radiation, for instance, 1 rem = 10 rad.

Rb^{86}. A radioactive isotope of Rubidium which disintegrates with a half life of 19 days by emitting high energy beta and gamma radiation.

Scanning. In order to determine the location, shape and intensity of a radioactive deposit, a collimated radiation detector (see "Collimation") is moved over the deposit in some regular fashion by an automatic transport mechanism; the counting rate at each point is plotted on a chart by some graphic means, for instance, by dots. The area of interest is scanned by the mechanism and the chart gives a visual representation of the radioactive deposit.

Scintillation counter. A highly sensitive device for detecting nuclear radiation. Some crystals have the property of emitting flashes of visible light when they absorb nuclear radiation. These light flashes are converted into electrical pulses by a photomultiplier tube. The electrical pulses are counted like pulses from a Geiger Mueller counter.

Na^{24}. A radioactive isotope of sodium which disintegrates with a half life of 15 hours by emitting high energy β and γ radiation.

Sr^{85}. A radioactive isotope of Strontium which disintegrates with a half life of about 2 months by emitting medium energy γ radiation.

Total body radiation. The radiation dose in rads (see "rem") received by

the whole body of man or animal when the body or a specific organ is irradiated externally or by internal administration of a radioactive substance.

Tritiated water. Water in which ordinary hydrogen is replaced by Tritium, the radioactive isotope of hydrogen.

Tritium labelled water. Water which contains some measurable amount of tritiated water.

Tritium, H^6, a radioactive isotope of Hydrogen which disintegrates with a half life of 12½ years by emitting very low energy β radiation.

The Use of Radioisotopes in Clinical Studies of the Central Circulation

By EUGENE BRAUNWALD, ANDREW G. MORROW AND ROLAND FOLSE

IN 1927 BLUMGART AND WEISS injected radium C into the antecubital veins of patients with heart disease and detected its appearance in the other arm by means of a modified cloud chamber. By this new approach, these investigators measured the "circulation time" between the systemic venous and arterial beds and, for the first time, utilized a radioactive substance in the clinical study of the circulation.[1] Since this pioneer investigation was carried out, the increasing availability to medical investigators of a number of isotopes, the development of a variety of efficient radiation detectors, and the widespread use of dye dilution curves[2] and of inert foreign gases[3] have all set the stage for the increasing applications of radioisotopes in methods of studying the circulation.

During the past several years, observations in a number of laboratories have demonstrated the clinical usefulness of radioisotopes in several specific applications. At the National Heart Institute isotopes are now employed for the precise characterization of left-to-right[4] and right-to-left circulatory shunts,[5] for the measurement of cardiac output,[6] and for determining the fraction of the ventricular end-diastolic volume discharged per beat as well as the ventricular end-diastolic volume.[7] In addition, they are utilized for detecting the presence or absence of left-to-right shunts without cardiac catheterization.[8] In the present review the technics and applications of these clinical studies are summarized.

Inhaled Kr^{85} in the Study of Left-to-Right Circulatory Shunts

In 1945 Kety and Schmidt demonstrated that following the onset of the inhalation of an inert foreign gas (nitrous oxide), its concentration in arterial blood rises rapidly while the concentration in venous blood rises more slowly. Only after several minutes of inhalation does the venous concentration approach the arterial.[9] These investigators utilized this finding in the development of a useful method for the estimation of cerebral blood flow, and by appropriate modification of the site of venous sampling, the same principle has been applied for estimation of coronary blood flow[10] and of blood flow in other regions of the body. Inhalation of an inert foreign gas, with sampling of arterial and venous bloods may also be utilized in a somewhat analogous manner, for the assessment of left-to-right circulatory shunts, as illustrated in figure 1.

Our initial experiences with inert foreign gases were with nitrous oxide[11-13] but the concentration of krypton-85 may be much more rapidly and accurately assayed in blood than nitrous oxide, and for this reason it has supplanted

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