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Review Article

Radiopharmaceuticals

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TWO MAJOR developments occurred in 1940–1946 that revolutionized the methodology of research involving biological systems, by lowering the amounts of materials detectable to the microgram and submicrogram level. They were the chromatographic methods of separation and the availability of radioactive nuclides for the labeling and tracing of molecules and submolecular fragments. These tools were rapidly applied in all areas of biological research, including the diagnosis of disease. The use of radionuclides in the diagnosis and therapy of disease created the new specialty of nuclear medicine, and the specific drugs used in this specialty are called radiopharmaceuticals. The birth of nuclear medicine, and the concomitant development of radiopharmaceuticals, predate the creation in 1946 of the United States Atomic Energy Commission.

The first use of radioactive nuclides in man is to be credited to Blumgart and Yens (1), who in 1927 measured circulation (in man), after injection of a saline solution that had been exposed to radon, using a cloud chamber as the radiation detection device. The isotopes available at the time were only those belonging to the natural uranium, thorium, and actinium series, which limited their use in clinical work. The discovery, by Joliot and Curie (2), that other nuclides could be produced artificially, and the subsequent syntheses, by nuclear transmutation, of hundreds of artificial radioactive nuclides (3, 4), provided the tools for their biological and clinical use.

The use of ^{128}I by Hertz, Roberts, and Evans (5) in 1938, for the study of thyroid function, marks the real beginning of the systematic clinical use of radionuclides. Developments since then have been astronomical, and they have been thoroughly reviewed by Christian in 1961 in *J. Pharm. Sci.* (6) and by many others elsewhere since (7–51). Of special interest are the proceedings, published in April 1966, of the November 1965 Oak Ridge Conference on radiopharmaceuticals (30).

The development of a new science can usually be divided into several phases. First, there is discovery, and there are hopes that the possibilities of the new tool will be nearly unlimited. In the second phase, problems begin to be better appreciated and the initial enthusiasm is somewhat abated. And in a third phase, the new field achieves maturity, becomes fully aware of its potential and limitations, and achieves considerable sophistication.

Radiopharmaceuticals have entered this third phase. Thus, while originally tests were devised to make use of available radionuclides, now new

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nuclides are being produced to meet the specific requirements of half-life, emission characteristics, and chemical properties tailored to a specific test. Pinajian has stated that most of the over 1000 nuclides known can now be prepared by reactor (52), cyclotron (53), or related processes (54). We will first discuss the radionuclides that have proven useful in nuclear medicine, and the radiopharmaceuticals that contain them.

Radioactive nuclides are measured by the radiation they emit, and considerable progress has been achieved in the instrumentation used in nuclear medicine. Solid-state circuitry has often decreased the size and weight of instruments to a fraction of the older tube models, and increased their accuracy and reliability. Special tools have been developed to measure specific radiopharmaceuticals in specific diagnostic tests. Thus, highlights of new instrumentation and their relevance to radiopharmaceuticals will be considered next. Following will be a discussion of the application of radiopharmaceuticals in clinical medicine, production, and use in ancillary areas.

If we define a pharmaceutical agent as a compound used in the diagnosis, mitigation, or therapy of a disease, then a number of chemical entities containing a radioactive nuclide meet these requirements. Such compounds are called "radiopharmaceuticals," and our present discussion is to be limited to recent advances in the nature, preparation, and detection of such labeled materials. We will thus not cover many other very closely related (and sometimes overlapping) areas, such as clinical use of radiation (55) (except when radiopharmaceuticals are used as therapeutic agents), activation analysis of biological materials (56–61), radiochemistry (62–65), radiobiology (66–69), Mossbauer effects (70–71), radiological health (72–75), and others (76–83).

While radiopharmaceuticals differ from other pharmaceuticals only in that they contain a radioactive nuclide, they have generally not been handled by pharmacists. This is due partly to historical reasons (radiopharmaceuticals are usually handled and dispensed by, or under the supervision of, the radiologist or the radioisotope department) and partly to lack of training. However, the number of schools of pharmacy that have radioisotope training in their curricula is increasing and it is hoped that a greater number of pharmacists will become more actively involved in dispensing radiopharmaceuticals (32) once they have adequate training.

Radiopharmaceuticals offer the pharmacist an unusual opportunity for returning to the type of work that was his own years ago, and for which he is still being trained—namely, that of preparing and compounding a pharmaceutical, not just repackaging a completely finished preparation. This is especially true if we consider that there are definite advantages in preparing radiopharmaceuticals at the place of use, particularly those containing many of the "short-lived" radionuclides (see below). The possibility that radiopharmaceuticals may be handled at the retail level (32) is remote, as labeled products cannot be properly transported, stored, and handled except in restricted areas.

DEFINITIONS, TERMS, AND NOTATIONS

While it is assumed that the reader has a working knowledge of radioactivity (62), certain terms and symbols pertinent to this field require some clarification. For more detailed glossaries and dictionaries, the reader is referred to *References 84–87.*

A *nuclide* is a unique atomic species, characterized by its atomic number Z, mass number A, and energy.

Nuclides can be stable or can suffer radioactive decay. Thus, hydrogen has a stable isotope, the nuclide ^{2}H (or D), deuterium, and a radioactive isotope, the nuclide tritium ^{3}H (T). As the term *isotope* has been used in a broad sense, and leads to some confusion when such terms as "isotopic purity," etc., are used, the more precise term nuclide is now being generally adopted.

Atomic species having the same atomic number but different mass numbers are *isotopes;* and atomic species having the same mass *and* atomic numbers, but differing in the energy content of the observable state, are called *isomers* (*e.g.*, ^{99m}Tc and ^{99}Tc, where m denotes metastable).

Radioactive decay is characterized by four parameters. (*a*) The half-life of the radioactive nuclide, *e.g.*, the time necessary for 50% of the material present to decay ($T_{1/2}$). (*b*) The nature of the radiation, *e.g.*, α, β^- (negatron), β^+ (positron), and γ radiation. Of interest also are such phenomena as EC (electron capture) and IT (isomeric transition). (*c*) The energy of the radiation emanating from the nuclide upon decay. (*d*) The nature of the nuclide remaining *after* the radioactive decay process (daughter element).

From a clinical point of view, it is desirable to use labeled molecules *in vivo* for only such time as is necessary and no longer, so as to minimize radiation exposure. For this reason, the terms "long-lived" and "short-lived" are very much used, but they have different meanings according to the interests of the user. Furthermore, in *in vivo* work, we do not have to consider only the physical half-life, T_p, but also the biological half-

life, T_b. This leads to the "effective" half-life T_e (19). We propose the following definitions of effective half-lives for radiopharmaceutical work.

"Very short-lived," T_e less than the duration of the clinical procedure.
"Short-lived," T_e equal to and up to 3 times the duration of the clinical procedure.
"Long-lived," T_e greater than 5 times the duration of the clinical procedure.

These definitions differ from those generally used chemically, where only the physical $T_{1/2}$ is relevant, and where nuclides of less than 2–3 months are considered "short-lived," and where "long-lived" applies to ^{14}C ($T_{1/2}$ = 5720 years) and similar nuclides (88).

Problems raised by the lack of precision in the terminology of radionuclides were carefully analyzed at the Oak Ridge Conference (30) especially by Cohen (89). Thus, while the International Union of Pure and Applied Chemistry adopted in 1952 and 1958 (90) the convention that the mass number is to be written as the *left superscript*, (*e.g.*, ^{14}C, *not* C^{14}), many authors still continue to use in 1967 the older (and incorrect) symbol. Much confusion also arises in the nomenclature of labeled molecules used as radiopharmaceuticals. Thus, U.L. stands for "uniformly labeled," meaning molecules usually obtained by a biological procedure where all the atoms of a given element are labeled with the same specific activity (88, 91). This is not to be confused with random labeling, *e.g.*, when a product is exposed to tritium by the Wilzbach technique (92–94), where large variations can occur in the specific activity of different chemical functions. Several lists of U. S. adopted names (USAN) have been published in the *Journal of the American Medical Association* (95).

Another source of confusion is the term "carrier free." A stable nuclide, *e.g.*, ^{127}I, is often added as a "carrier" to trace amounts of the radioactive nuclide ^{131}I. Sometimes this dilution is intentional, and sometimes it is inherent in the procedure of isolation and purification of the radionuclide (88, 96, 97). Thus, "carrier free" has been used alternatively to mean "no carrier added," and "no carrier present." To avoid confusion, when it is meant that no carrier has been added, it should be so stated (98). Furthermore, the nuclidic composition should be given. For a discussion of radiochemical, chemical, and radioisotopical purity, see under *Manufacture of Radiopharmaceuticals*. Another important designation is the *specific activity* of the radiopharmaceutical, defined as activity [in curies (c.) or fractions thereof] per unit weight or volume. Specific activities are often expressed as mc./m*M*, μc./mg., or μc./ml. A high turnover and a highly exchangeable biological pool of the material under study requires materials of high specific activity, especially in the newly developing field of radioimmunoassay (99, 100). The importance of a careful consideration of biochemical relationships, such as turnover, exchangeable pools, etc., has been carefully discussed by Bayly (101). The chemical stability or exchangeability of the radionuclide of the tagged radiopharmaceutical is also important to ensure the reliability of the chemical diagnosis (102, 103). Thus, many tagged products have a short shelf-life, and should be freshly analyzed before usage (104).

RECENTLY INTRODUCED RADIOISOTOPES AND THEIR COMPOUNDS FOR USE IN NUCLEAR MEDICINE AND PHARMACY

The use of radiopharmaceuticals in diagnostic nuclear medicine and therapy falls into several, not too rigidly defined, categories as shown in Table I. These illustrate the diversity of the uses and recent developments in radiopharmaceuticals.

Of the 102 elements and about 1,000 nuclides of these, only nine nuclides of six elements comprise 70% of the medical uses. These are ^{131}I, ^{51}Cr, ^{125}I, ^{99m}Tc, ^{132}I, ^{22}Na, ^{85}Kr, ^{197}Hg, and ^{203}Hg (31).

TABLE I.—SCOPE OF RADIOACTIVE TRACER METHODOLOGY IN BIOLOGY AND MEDICINE

Isotope Dilution	Diffusion and Flow	Metabolic Studies
Body compn., *e.g.*, total body K and H_2O.	Spatial distribution as in organ and whole body scanning.	Metabolism of amino acids *e.g.*, ^{75}Se-methionine.
Body spaces, *i.e.*, volumes of distribution, *e.g.*, chloride and hormone spaces.	Positive and negative concentration in organs and tissues by space-occupying structures.	Metabolism of carbohydrates, drugs, hormones, lipids, minerals, and proteins.
Body fluid volumes, *e.g.*, blood and plasma volumes.	Cardiac output.	
Exchangeable body elements, *e.g.*, Na and K.	Cell membrane absorption and permeability.	
	Regional circulation, *e.g.*, coronary, hepatic, and renal.	

A radiopharmaceutical or substance used in nuclear medicine is characterized by four major parameters: (*a*) its sojourn or time-course within the organ or lesion under study, relative to other structures as in tumor or organ scanning, (*b*) the type and rate of radioactive decay, (*c*) its detection characteristics, and (*d*) its production and preparation (31).

In view of the above parameters, it is readily understandable why the development of new radiopharmaceuticals has been in the direction of the use of compounds containing short-lived nuclides, preferentially those which produce only γ or positron radiation. These radionuclides provide radiation adequate for scanning with little or no useless and undesirable β radiation, and have only a short physical half-life, thereby yielding minimal total body or regional radiation.

Presently there are 32 γ or positron emitting radionuclides used in nuclear medicine, either as their inorganic salts, or as organic compounds. These nuclides vary in physical half-life from 1 hr. for ^{68}Ga to 10.3 years for ^{85}Kr (31). A major drawback in the development of nuclear medicine has been the limited ability to synthesize appropriate radiopharmaceuticals with definite biochemical behavior incorporating these short-lived radionuclides.

However, as an example of the successful preparation of such compounds, ^{99m}Tc with a physical half-life of 6 hr. and emitting only desirable γ rays for scanning, has been incorporated extemporaneously into several compounds with desirable biological behavior. These compounds are ^{99m}Tc-labeled human serum albumin as a sol (105) for placental scanning (106); as a macroaggregate of several particle sizes for distribution and scanning the liver and spleen and lung (107).

Several other ^{99m}Tc compounds have been prepared: colloidal ^{99m}Tc-sulfide has been used for liver scanning (108); ^{99m}Tc-thiocyanate dispersed in an injectable fat emulsion (109, 110) has also been used as a liver scanning agent. The pertechnetate, $^{99m}TcO_4^-$, has found wide acceptance as an agent for brain tumor scanning (110), for determining the trapping index of the thyroid (111), and for scanning the thyroid (112).

Technetium-99*m* is prepared as sodium pertechnetate by eluting or "milking" the generator or "cow" in which it is formed by the decay of ^{99}Mo which has a half-life of 2.8 days. Thus, the ^{99}Mo can be prepared at a reactor site or cyclotron, separated, and shipped as a "cow" and the ^{99m}Tc prepared extemporaneously.

Similarly, other generators are available for the production of other potentially desirable and useful short-lived radionuclides as radiopharmaceuticals. Six other generators are presently available—namely, ^{132}Te yielding ^{132}I (96); ^{87}Y yielding ^{87m}Sr (96); ^{137}Cs yielding ^{137}Ba (113); ^{68}Ge yielding ^{68}Ga (96); ^{113}Sn yielding ^{113m}In (54); and ^{103}Pd yielding ^{103m}Rh (54).

Iodine-132 is produced by decay of the parent ^{132}Te which has a $T_{1/2}$ of 3.2 days. Iodine-132, $T_{1/2}$ of 2.33 hr., has been used as the iodide for thyroid scanning and uptakes, especially in children and pregnant women in order to minimize the radiation dosage to the thyroid gland (114).

Other radioiodine isotopes have been proposed (115) for studies of thyroid physiology, measurement of uptake, and scanning based on short physical half-life and lack of undesirable radiation, but ^{131}I continues to be used most generally (114, 115).

In consideration of the parameters stated above for a radiopharmaceutical and the principle of minimum radiation dosage to the patient, the development of ^{57}Co-labeled cyanocobalamin (vitamin B_{12}) is exemplary.

Schilling (116) in 1953 devised a test for pernicious anemia using cyanocobalamin containing ^{60}Co. The liver is the repository of any unexcreted cyanocobalamin Co 60 and thus becomes the critical organ of exposure, especially since the biological half-life was shown to be from 315 to 450 days (117). In order to reduce the radiation received by the liver other radioisotopes of cobalt were sought which would reduce the radiation, and ^{57}Co appears best (118). By the substitution of ^{57}Co, the radiation dose to the liver is reduced to $^1/_{29}$th of that delivered by cyanocobalamin Co 60, a very desirable result.

In an attempt to reduce the radiation delivered to the kidneys during scanning of these organs (119) and also as a result of brain scanning using radioactive mercury-labeled chlormerodrin, ^{197}Hg has been substituted for ^{203}Hg in this compound (120). Since the $T_{1/2}$ of ^{197}Hg is 2.7 days *versus* a $T_{1/2}$ of 47 days for ^{203}Hg, the radiation dose is markedly reduced (28).

Recently, 1-mercuri-2-hyroxypropane labeled with ^{197}Hg has been proposed for scanning the spleen (121). This substance binds tightly to the red cells and damages them, so that now these damaged red cells are sequestered by the spleen, providing a tool for scanning that organ.

The spleen can also be scanned successfully by the use of red cells which were previously treated with sodium chromate Cr 51 and subsequently heat-damaged, resulting in their sequestration by that organ (122).

An example of the development of a new agent for scanning the pancreas for inflammation, car-

cinoma, and morphological abnormalities is that of ^{75}Se-L-methionine. This selenium analog of methionine is incorporated rapidly into pancreatic tissue with as much as 7% being incorporated in this organ and with a pancreas to liver ratio of concentration of 8:1 (123). Selenium-75 has a $T_{1/2}$ of 128 days and a principal γ ray energy of 0.27 Mev., quite suitable for scanning.

More recently ^{75}Se-L-methionine has been proposed as an agent for scanning the parathyroid gland (124). It was found that after injection, the activity in the parathyroids was 2 to 3 times higher than that found in thyroid, muscle, and blood. Adenomata were successfully located preoperatively, but this method awaits further clinical establishment.

In recent years attempts have been made to develop new radiopharmaceuticals for assessing the biochemical functions, or for delineating morphological structures, based on biochemical or physiological principles. The use of ^{131}I-labeled iodohippuric acid for kidney function testing and scanning was based on the well known conjugation and elimination of benzoic acid in the form of hippuric acid, and the established rapid renal tubular secretion of iodohippuric acid (125). Sodium Iodohippurate I 131[1] has become the agent of choice for renal function testing and has found wide use as an agent for measuring differential renal blood flow, coronary blood flow, and for many other dynamic fluid physiological studies. This compound is included in the U.S.P. XVII (126).

When no suitable radioisotope of an element is available, as is the case with chlorine, it has been possible to substitute one chemical element for an analog. This is exemplified by the use of ^{82}Br, as the bromide, instead of the chloride ion. Bromine-82 with a $T_{1/2}$ of 36 hr. has essentially the same body distribution as chloride and is used as an acceptable and reliable measure of the extracellular distribution of the latter (127).

Similarly, ^{86}Rb has been used to measure exchangeable potassium and suitable clinical methods have been developed (128).

In line with the thinking that minimal radiation to the patient is optimal, recent developments are the *in vitro* tests, as, for example, those used for thyroid function. In these tests, no radioiodine is administered to the patient; rather, the test is performed on the patient's serum, permitting even serial tests of children and pregnant females. These tests use L-iodothyronine I 131 and anion-exchange resins; more recently, the resin has been incorporated in a polyurethane sponge, thus simplifying the test and allowing greater reproducibility (129). Other techniques using anion-exchange resins to replace the red cells, as proposed by Hamolsky *et al.*, are also available (130).

A promising field of development likely to be expanded in the future is the preparation of chelates of many short-lived radionuclides. As an example, ^{197}Hg has been chelated with calcium and ethylenediaminetetraacetic acid for use in kidney scanning (131). It is selectively secreted by the renal cortex and the radiation dose to the patient is somewhat less than that from a much smaller dose of chlormerodrin Hg 203.

Heretofore, studies of magnesium, a biologically important element, have been hampered. Recently, however, ^{28}Mg with a half-life of 21.3 hr. became available with high specific activity. Extensive investigations of magnesium metabolism, such as exchangeable Mg in animals and in man, have been made possible (132, 133).

Recent advances in scanning techniques of great importance in nuclear medicine were coincident with the development of new radiopharmaceuticals and new forms of previously used radiopharmaceuticals. In "scanning," the delineation of the size, shape, location, or morphological characteristics of an organ or structure are indicated by a diagrammatic or photographic (light or dark) rendition of the localization of the radionuclide or its compound. It is obvious that radiopharmaceuticals, trophic to these structures by virtue of their biochemical or physiological characteristics, are desired.

Recent developments have occurred with the introduction of macroaggregates of human serum albumin containing radioiodine for scanning the liver, lung, and spleen (106, 107) and several compounds of ^{99m}Tc (108–111) for similar purposes; diuretics containing radioactive mercury for brain and kidney scanning; labeled amino acids for incorporation into organs rapidly synthesizing proteins, as for example, the use of ^{75}Se-L-methionine in pancreas scanning; and the labeling of erythrocytes with ^{51}Cr or 1-mercuri-2-hydroxypropane-^{203}Hg or MHP-^{197}Hg for spleen scanning (121).

The development of therapeutic radiopharmaceuticals is paralleling the development of diagnostic agents. As an example, ethiodized oil[2] I 131, which consists of the ethyl esters of the iodized fatty acids of poppy seed oil, has been prepared containing approximately 5 mc. ^{131}I

[1] Marketed as Hippuran I 131 by Volk Radiochemical Co.

[2] Marketed as Ethiodol by E. Fougera & Co., Inc., Hicksville, L. I., N. Y.

per ml. Following intralymphatic infiltration this material delivers therapeutic irradiation to pathological lymph nodes and can be used alone or in conjunction with irradiation for the destruction of malignant lymphatic tissue (134, 135).

Recent additions to the armamentarium of radioisotope therapy are the radioactive colloids. Yttrium-90, an almost pure β emitter with a half-life of 65 hr., is "milked" from a ^{90}Sr generator. The ^{90}Y is converted to the chloride which hydrolyzes at a pH of 7.0 to 7.8 and behaves like a colloid. It has been used to treat malignant serous effusions (136). Colloidal yttrium fluoride and hydroxide have been proposed also for use in yttrium therapy.

Recent investigations of the use of ^{131}I combined with colloidal size ion-exchange resins have been made for use in localized treatment of some types of cancer (136).

Radioisotopes for diagnostic and therapeutic uses have been prepared in a variety of dosage forms. (See Tables II and III.)

Capsules containing radioisotopes for diagnostic and therapeutic purposes were designed as a safe and effective method of administration (137) and are presently widely used for several labeled materials.

Radioiodinated human serum albumin is available in standardized doses in plastic disposable syringes from several suppliers. These can be used in conjunction with digital computing equipment for rapid blood volume determinations based on the principle of isotope dilution (138).

Most radioactive chemicals for use in nuclear medicine have been chosen on the basis of the characteristics of the radioisotope contained or its chemical or physical form, rather than its biological behavior or sojourn.

Only four commonly used radiopharmaceuticals can be classed as "biochemicals" and are used on the basis of their biochemical behavior (101). They are: labeled cyanocobalamin, thyroxine, triiodothyronine, and ^{75}Se-labeled selenomethionine.

According to the authors, a similar justifiable inclusion would be the labeled ions of iodide, phosphate, calcium, and those of some trace metals.

Obviously, there is need for the development of radiopharmaceuticals resembling natural biochemicals, which could be incorporated in tissues and biological structures. Such radiopharmaceuticals should have desirable characteristics for their detection in nuclear medical procedures. With the development of newer and simpler techniques for assaying ^{14}C and ^{3}H compounds, labeled analogs of natural biochemicals will find ever-increasing use in nuclear medicine.

METHODS OF DETECTION

When radionuclides decay they emit one or more types of radiation: α (helium nuclei), β^- (negatrons), β^+ (positrons), γ or X-rays. These radiations are able to ionize matter and produce ion-pairs. Thus, one method of detection of radioactive decay is based on the collection and measurement of the ions produced by the ionizing radiation. Such an instrument is the Geiger-Mueller (G.M.) tube. A second method of detection is based on the fact that certain molecules will absorb energy and not become ionized, but instead undergo a transition to an excited state. The decay of that excited molecule to the ground state is accompanied by the emission of electromagnetic energy, usually in the ultraviolet or visible range of the spectrum. This light pulse is converted by photomultipliers to an electrical pulse which is then measured. These techniques are called scintillation detection methods, and are the most widely used in the measurement of radionuclides of clinical interest. New methods of detection using semiconductor or solid-state detectors are being developed (139), but they are not yet used clinically to any great extent.

A fourth method of detection is based on chemical reactivity, with, for example, silver halides in photographic emulsion. Photographic methods of detection such as autoradiography are extensively used in pharmacology.

For a more detailed discussion of detectors, the reader is referred to Price (139). Recent progress in solid-state detection, which may become very useful for measurement of low energy γ emitters such as ^{125}I and ^{197}Hg, has recently been reviewed (140, 141).

Perhaps the most important development in the last 10 years has been the introduction of solid state electronics. Thus, large and bulky tube models have been replaced by more efficient, reliable, and compact solid-state electronic systems. For a full discussion of these topics, see Yanof (142) and Malmstadt (143).

Most radionuclides of biological interest are either β^-, γ, or β^+ emitters; practically no radionuclide of clinical interest is an α emitter. β^- Radiation is very easily absorbed by tissue, and does not lend itself easily to dynamic clinical studies of deep-seated organs. Best suited are radionuclides emitting γ radiation, either by direct decay, as a result of β^+ annihilation (the $T_{1/2}$ of the positron is 1.5×10^{-10} sec.) or X-rays emitted after electron capture. γ Radiation is

best detected by scintillation type detectors, and most instrumentation used in clinical work utilizes them.

The radiopharmaceuticals most widely used are discussed below. They are used in the visualization of organs for space-occupying defects, to assess their function, and to determine dynamic changes in body constituents.

Scanning was first utilized to visualize the thyroid gland (144) and has since developed into a most important procedure of nuclear medicine. Several comprehensive reviews cover the subject (145–147).

When a labeled compound localizes preferentially in an organ, *e.g.*, I^- in the thyroid gland, the intensity of the radiation emanating from each part of the organ under study will be proportional to its physiological state. Thus, a nonfunctional nodule will appear to concentrate less radioactivity, whereas a hyperfunctional area will concentrate a larger amount of the radiopharmaceutical.

A scanner is a scintillation detector, capable of moving mechanically over the area to be studied. A scanning system is composed of: (*a*) a detector, (*b*) a collimator and shield, (*c*) a mechanical movement device, (*d*) data presentation and display.

The original thyroid scanning detector used a $^1/_4$-in. crystal (144); the efficiency of such a system was low, and presently crystals of 2 × 2 in. and 3 × 2 in. are used routinely, with an increase in efficiency of over 100-fold. Larger detectors need larger shielding and efficient collimation, and much effort has been devoted to improving the quality of focusing collimators (148). Furthermore, the increase in shielding and in collimation increases the weight of the scanning device, creating severe mechanical problems. Further details on scanning devices can be obtained from several major manufacturers of such equipment.

A major effort has been devoted to improvement of data presentation. The original dot scan, giving series of black dots on white paper, has been considerably improved for greater ease of interpretation of the results obtained. Thus, Kakehi *et al.* (149) developed a device whereby the impulses from the spectrometer were fed into a strobo-tube, with different colors representing increasing intensities. A similar device is the photorecorder of Adams and Jaffe (150).

While scanning devices are still extremely important, they have several disadvantages, such as the long time needed to complete a scan and the high dose of radionuclide needed. A new approach is that of the scintillation cameras, first developed by Anger (151). The large crystal detector views the whole organ, and the scintillations are transmitted to a battery of small phototubes. The whole organ is thus seen in its entirety, reducing the time necessary for a single scan, allowing a dynamic observation of the organ, the use of nuclides of shorter half-life, etc. (152).

Several models of such cameras have been developed. The original Anger camera (151) consists of a single large crystal. A modification of the scintillation camera is the Autofluoroscope of Bender and Blau (153), consisting of a mosaic of several hundred scintillators. A third instrument has been described by Ter-Pogossian (154) which consists of a fluorescent screen and a specially designed image amplifier tube.

More recently, much interest has been raised by spark-chamber types of devices, such as the Spintharicon (155), the spark-chamber of Kellershohn (156) and the cross-wire spark-chamber (157), usable for both β and γ counting.

Decay by positron emission is followed in 1.5×10^{-10} sec. by positron annihilation, producing 2 photons of 0.51 Mev. each, that are emitted at an angle of 180°. The use of two scanners, 180° apart, or of two scintillation cameras, also 180° from each other, has been used for brain tumor localization (158), although conventional γ scanning appears to be equally effective.

Certain nuclides, such as ^{40}K, are distributed throughout the body. Their level can best be measured by whole body counters. These can be either of the NaI type, with one or more detectors (159–161), or of the liquid scintillation type first described by Anderson *et al.* (162). More recently, a system has been described with 18 organic plastic detectors employing 72 photomultiplier tubes, able to determine whole body counts as well as localization in organs (163).

Thus, a highly sophisticated array of instrumentation exists and is being developed for the measurement of radionuclides *in vivo*. As will be seen below, the next great advance in this field will come by the use of other radionuclides, which according to Stang can be "tailored to will" (164), and by a thorough understanding and application of biochemical and pharmacological principles applied to radiopharmaceutical drug design (31, 101).

Also, the development of clinical tests using ^{14}C and ^{3}H-labeled compounds has been made possible by improvements in counting techniques such as the liquid scintillation counters (139, 165, 166).

CLINICAL APPLICATIONS

The clinical applications of radiopharmaceuticals are divided into two main categories: (*a*) those used in diagnostic procedures and (*b*) those used for therapy. An extensive survey of these uses is beyond the scope of this review and the reader is therefore referred to some very excellent recent source material (14, 29, 31, 38, 167–169). However, the general lines of research and development will be presented here.

The improvement and simplification of counting techniques and equipment for weak β emitters has resulted in the use of ^{14}C and ^{3}H-labeled compounds in medical and biomedical techniques. Tritiated water is now widely used in the determination of total body water (170). Uniformly labeled ^{14}C-glucose has been used to study glucose kinetics in normal, diabetic, and acromegalic subjects (171). In this study the quantities of expired CO_2 and $^{14}CO_2$ in the mixture were monitored (172) and deviations from the normal range for the diabetic and the acromegalic subjects were observed.

Studies of fat absorption, using ^{131}I-labeled triolein, are open to serious question because the iodinated triolein is not a single compound, and frequently contains impurities. These have also been labeled, but they do not behave biologically like triolein (173). It is absolutely necessary to separate the labeled triglyceride from the other materials using techniques such as thin-layer chromatography and gas–liquid chromatography, both in their analytical and preparative aspects. It is incumbent upon the investigator to prove the purity of his materials so as to eliminate any uncertainty in the clinical test. Some investigators using the commercially available ^{131}I-labeled triolein in an empirical manner have obtained consistent results suitable for diagnostic purposes.

It has been argued that an iodinated, or an iodinated and chlorinated, fat or fatty acid no longer behaves biologically like the original fat or fatty acid, and only ^{14}C-labeled lipids prepared by biosynthetic methods truly resemble the unlabeled fat. This subject was recently reviewed (174).

Tables II and III illustrate the diversity of composition of some radiopharmaceuticals used in nuclear medicine. The doses given are variable, depend on the equipment and technique used, and are thus only approximate. The references

TABLE II.—DIAGNOSTIC USES OF RADIONUCLIDES

Radiopharmaceutical[a]	Diagnostic Use	Dose, μc.	Ref.
Sodium Iodide I 131	Thyroid uptake and excretion studies	1–20	(114)
	scanning thyroid gland	50–300	(175)
Liothyronine I 131 or I 125 (L-Triiodothyronine I 131 or I 125)	*In vitro* studies of thyroid function (resin and red cell uptake tests)	1 or less	(129, 176)
Iodinated Human Serum Albumin I 131 or I 125	Blood and plasma volumes	3–20	(177)
Macroaggregate Iodinated Human Serum Albumin I 131 or I 125	Lung, liver, and spleen scanning	200–300	(178)
Sodium Iodohippurate I 131 or I 125	Kidney function	10–50	(125, 179)
Rose Bengal I 131 or I 125	Liver function	10–25	(180)
	Liver scanning	100–150	(181)
Oleic Acid I 131	Fat absorption studies	25–50	(182)
Triolein I 131	Fat absorption studies	25–50	(183)
Tritiated Water	Total body water	500–2000	(170)
Sodium Phosphate P 32	Detection of eye tumors	250–500	(184)
Calcium Chloride Ca 47 or Ca 45	Distribution and metabolism	1 μc./Kg.	(185)
Sodium Chromate Cr 51	Red cell mass and volume	10–25	(186)
	Red cell survival studies and spleen scanning	75–150	(187)
		150–300	(122)
Cyanocobalamin Co 57 Cyanocobalamin Co 58 Cyanocobalamin Co 60	Pernicious anemia and malabsorption syndromes	0.25–1	(188)
Gold Au 198	Liver tumor localization	300	(189)
Ferrous Citrate Fe 59	Oral iron absorption	5–10	(190)
	Plasma iron turnover and disappearance	5–10	(191)
	Iron utilization and turnover	5–10	(192)
^{99m}Tc Sodium Pertechnetate	Brain tumor scanning	10,000	(110)
	Thyroid uptake	1000	(111)
^{99m}Tc-Labeled Human Serum Albumin	Placental scanning	1000	(106)
^{99m}Tc-Technetium Sulfide	Scanning liver and spleen	2000	(108)
Macroaggregates of ^{99m}Tc-Labeled Human Serum Albumin	Scanning liver and spleen	3000	(193)
	and lung	1500	(194)

[a] USAN names used where applicable.

TABLE III.—THERAPEUTIC USES OF RADIONUCLIDES

Radiopharmaceutical[a]	Therapeutic Use	Dose, mc.	Ref.
Sodium Iodide I 131	Hyperthyroidism	2–10	(195)
	Cardiac and pulmonary disease	25–50 divided doses	(196)
	Thyroid cancer	100–150	(197)
Sodium Phosphate P 32	Polycythemia vera	3–8	(198)
	Chronic leukemia (lymphatic or myeloid)	1–2 per week	(199)
	Metastatic bone cancer	10–15 divided doses	(200)
Chromic Phosphate P 32	Treatment of peritoneal effusions	10–15	(201)
	Treatment of pleural effusions	8–12	(201)
Gold Au 198	Treatment of pleural effusions	75–200	(202)
Gold Au 198 seeds or wires	Interstitial implantation into tumors	Variable	(203)
Cobalt 60 needles, seeds or wires	Interstitial implantation into tumors	Variable	(204)
	Treatment of tumors in body cavities	50–75	(204)
Strontium 90 applicators	Treatment of ophthalmological lesions	Variable	(205)
Iridium 192 seeds	Interstitial tumor irradiation	Variable	(206)
Tantalum 182 needles	Bladder tumors	Variable	(207)
Ethiodized Oil I 131	Intralymphatic radioisotope therapy		(134)

[a] USAN names.

are representative and not exhaustive. Names follow the USAN nomenclature (95) where available; otherwise common names are used. They are arranged very generally in the order of frequency of use. The reader is also referred to a more extensive table compiled by Silver (169).

MANUFACTURE OF RADIOPHARMACEUTICALS

Radioisotopes used in the preparation of radiopharmaceuticals and labeled compounds are prepared by prime producers who use reactors or cyclotrons. The products are then processed, purified, prepared in pharmaceutically acceptable forms, and assayed. They may be purified to meet the official requirements of the U.S.P. XVII (126) if standards have been established for such materials. These standards are minimal and many manufacturers have set their own more rigid specifications for identity and purity.

The provisions of the Federal Food, Drug and Cosmetic Act of 1938, as amended, apply equally to radiopharmaceuticals as to all other kinds of drugs (208).

Standards of purity, for example, as applied to usual pharmaceuticals are wholly inadequate with reference to radiopharmaceuticals. Some consideration of the necessary criteria for radiopharmaceuticals and their significance will be discussed here. *Chemical purity* is used in the customary sense to denote the presence or absence of chemical substances other than the desired single or multiple species. *Radiochemical purity* might be defined as the fraction of the stated radionuclide in the stated chemical form, as for example, sodium *o*-radioiodohippurate I 131 should not contain I 131 in the form of radioiodide or *o*-radioiodobenzoate. *Radionuclidic purity* refers to the proportion of the total activity in terms of the designated radionuclide. For example, chlormerodrin Hg 197 ($T_{1/2}$ = 65 hr.) prepared from irradiated naturally occurring mercury might contain ^{203}Hg amounting to 4% at the time of receipt. This amount of long-lived ^{203}Hg ($T_{1/2}$ = 46.9 days) is acceptable for immediate use, though undesirable. However, this level will have risen to 21% of the total activity at the end of 1 week and this is not acceptable. The use of enriched ^{196}Hg for the preparation of the ^{197}Hg used in formulating radiomercury diagnostic agents is an important development (209). The use of ^{197}Hg with its $T_{1/2}$ of 65 hr. is desirable for reducing the radiation delivered to the kidneys.

In addition to the criteria of purity, injectable solutions must meet the requirements of sterility, nonpyrogenicity, and all the other standards for parenteral products. While these are the responsibility of the original manufacturer, they apply equally to extemporaneous dilutions and subdoses as prepared in the hospital or nuclear medical clinic. Terminal sterilization in the final container or sterilization by filtration are most acceptable for radiopharmaceutical preparations.

Radiopharmaceuticals suffer radiolytic disruption and change, especially during storage, due to the radiant energy contained. Therefore, the nature and content of the products must be known. Inasmuch as the biological behavior of the split products may be entirely different from that of the desired material, clinical or scientific deductions would be erroneous. Radiopharmaceutical manufacturers therefore subject their products to analysis at the time of preparation, and after appropriate storage, to determine

"shelf-life" (210). Methods employed are column and paper chromatography and autoradiography, electrophoresis, γ spectrometry for radionuclidic purity and contamination, spectrography, chemical separations by the use of carriers, and others (89). Instability associated with radiolytic breakdown is dependent upon the energy of decay of the radionuclide, the specific activity, and the usual physical factors of light, temperature, solvent, oxygen, etc.

The reader is referred to an excellent review of quality control concerning the preparation, formulation, sterility procedures, and all other operations involved in production of radiopharmaceuticals and extemporaneous dilutions for a moderately large installation (104). Many of the procedures are equally applicable to small hospital and nuclear medical clinics (211).

In the manufacture of radiopharmaceuticals, antioxidants, buffers, antibacterial preservatives, stabilizers, and solvents are all required. The composition and reactivity of these materials are of prime importance.

The maintenance of sterility in radiopharmaceutical solutions is achieved by the addition of antimicrobial agents such as phenol, the methyl and propyl esters of *p*-hydroxybenzoic acid, and, most frequently benzyl alcohol. The choice of the bacteriostat is of utmost importance. It has been reported that benzyl alcohol, used in high activity solutions of radioiodide, reacted with the products of the radiolysis of water to form iodinated products, which showed a lower thyroid uptake and urinary excretion in rats after 4 hr., compared to a solution not so preserved (212). However, similar studies in humans have not been reported.

β-Naphthol used as a bacteriostatic agent in gelatin capsules for ^{131}I led to an iodinated β-naphthol as a radiochemical impurity, which made this pharmaceutical unsuitable for determining the function of the thyroid gland (89).

Antioxidants such as ascorbic acid, sodium ascorbate, cysteine hydrochloride, sodium sulfite, and thiosulfate are used to maintain radionuclides in the reduced form and at the proper valence state. Examples are ferrous citrate Fe 59 and sodium iodide I 131. In the case of the latter, solutions not properly protected against oxidation led to erroneous thyroid uptakes (213).

Buffers and stabilizers are added to radiopharmaceuticals to prevent the precipitation and reactions of the pharmaceutical with contaminants in the solution and from the glass containers. Sodium citrate has been used by the manufacturers to prevent calcium precipitation in some solutions. Great care must be exercised in the choice of additives to radiopharmaceuticals, so as to prevent precipitation and loss or removal of the minute quantity of the radionuclide present, or of inducing chemical changes in the nature of the tagged material.

Sterility is of prime importance in injectable radiopharmaceuticals. The problem is compounded by the short half-life of the radionuclide and the time required for an adequate insurance of sterility and nonpyrogenicity. The U.S.P. XVII (126) prescribes the methods to be used. The manufacturers have been permitted to release parenteral radiopharmaceuticals before the completion of the usual sterility test. Extensive testing, as well as the use of additional techniques, and a backlog of experience in the preparation of injectables, have insured an excellent record for the manufacturers. Many lots of radiopharmaceuticals, where the half-life and other factors do not preclude the preparation in advance of the required demand, allow for adequate sterility and pyrogenicity testing. The experience of one manufacturer, which is typical, is of interest (214).

The large-scale producers and manufacturers have been quick to translate the research findings of the radiopharmaceutical chemists and clinicians into practical production. Although they have not themselves developed new radiopharmaceuticals, they have made an enormous contribution in furthering the development, assisting research, providing materials for clinical trials, and conducting research on product improvement, dosage forms, and availability. The radiopharmaceutical manufacturers have offered "custom" services in the preparation of new materials such as iodination and tritiation as well as the preparation of specifically labeled compounds and intermediates and providing commercially unavailable radionuclides. Product improvement has taken the form of providing radiopharmaceuticals which yield less radiation such as in the substitution of the radionuclides ^{57}Co or ^{58}Co in place of ^{60}Co in preparations of radiocyanocobalamin, and of ^{197}Hg in place of ^{203}Hg in chlormerodrin.

The record of the manufacturers in making ^{99m}Tc available as "cows" and as rapidly delivered sterile solutions is impressive. Much credit is to be given to Brookhaven National Laboratories for developing and making available "cows" or generators for short-lived radionuclides before they were available from other sources (96).

The presentation of dosage forms of radiopharmaceuticals by the manufacturers has facilitated their use. Capsules, predated to contain definite doses at some specified time, single

and multiple dose vials, and unitary packages of sterile precalibrated doses in disposable syringes, are some outstanding examples.

Research and development has resulted in safe and convenient containers designed to minimize the radiation hazard to those engaged in handling and dispensing them. One manufacturer ships the products in outer containers made of polyethylene and lead which prevents shattering if dropped and also provides for complete drainage while held in such a container. Another major manufacturer provides bottles coated with a thick plastic covering to prevent shattering if the bottle is dropped or subjected to stress. Ease of opening both inner and outer containers has been provided by the manufacturers. Containers are adequately shielded for shipment and storage (167).

In 1946, 38 licenses were issued by the U.S.A.E.C. to medical institutions and hospitals to use radioisotopes and in 1955 this grew to 1149, while in September 1965, the number issued to medical institutions and physicians increased to 3600, in addition to about 1900 government laboratories and 500 colleges and universities, many of which were using radiopharmaceuticals and labeled compounds (215). From these figures the growth of the radiopharmaceutical industry is readily understandable. One large company has recently opened a new plant reputed to double its output of radiopharmaceuticals. It has been reported that the radiopharmaceutical industry has grown about 20% per year (216) and current sales are about $8 million per year (217).

There are several large American pharmaceutical companies and a number of smaller ones providing a wide range of radiopharmaceuticals, radionuclides of varying quality, and labeled compounds as well as special services. Much desirable reference material is available without charge from these companies, and the reader is urged to consult these sources.

Attempts have been made to prepare labeled drugs by exposure to a neutron flux, so as to induce the formation of radionuclides from some element present. As an example, probenecid [*p*-(dipropylsulfamyl)benzoic acid] was irradiated with fast and slow neutrons giving rise to ^{35}S and ^{32}P, both β emitters (218). There was much decomposition but pure material was isolated with a specific activity of about 12 μc./m*M* as ^{35}S. A trace of ^{32}P was formed and not removable. The distribution was studied in rats and found to accumulate mostly in the kidney. 5-Acetamido-1,3,4-thiadiazole-2-sulfonamide[3] was also irradiated by these same workers and a very pure product was obtained in a lower yield containing ^{35}S.

In the U. S. another group has reported the results of preliminary investigations of neutron irradiation of many compounds such as ethanol, nicotinic, phenylacetic, and salicylic acids, glucose, reserpine, and tetracycline. The instrumentation and techniques as well as the advantages and disadvantages are described (219). In these techniques radioisotopic yields are small and extensive purification of the products is required.

However, while recoil labeling has considerable limitations, it may be a very useful tool for the tagging of radiopharmaceuticals with radionuclides of very short half-life, such as ^{11}C ($T_{1/2}$ = 20.3 min.), ^{18}F ($T_{1/2}$ = 1.7 hr.) and others (220). As an example of at the site production of radiopharmaceuticals we can cite the work of Matthews *et al.* (221) on radioactive gases, used for respiration and lung function. They used ^{15}O ($T_{1/2}$ = 2 min.), ^{13}N($T_{1/2}$ = 10 min.), and ^{11}C.

RADIOPHARMACEUTICALS AND PHARMACOLOGY

"The use of isotopes in experimental pharmacology has facilitated investigations that without their use would have been cumbersome or difficult, and in other cases impossible to solve," states Roth (222). The pharmacologist has thus been able to make good use of the extraordinary tool provided by labeled compounds (drugs). It might also be safe to say that practically all new pharmaceuticals that are being studied today are labeled at some stage of preclinical testing, to study their biotransformation and other parameters of biological significance. A recent symposium has been devoted to Isotopes in Experimental Pharmacology (223), and this specific topic was reviewed in *J. Pharm. Sci.* a few years ago (224) as well as elsewhere (225–228).

Perhaps the greatest use of labeled compounds is in the study of drug metabolism and biotransformation. The information that can thus be obtained is: (*a*) rate and route of elimination; (*b*) biotransformation: number, nature, and rate of elimination of metabolites; (*c*) localization and penetration of a drug and its metabolites in organs and on specific subcellular structures; (*d*) identification of any "active" metabolite, and evaluation of its pharmacological action.

It is impossible to list here all metabolic studies of drugs elucidated with the aid of radionuclides; the following examples will serve to illustrate the potentials of such techniques.

[3] Marketed as Diamox by Lederle Laboratories, Pearl River, N. Y.

Phenobarbital is excreted either unchanged or as conjugated derivatives, as established after a study of the fate of 2-^{14}C-phenobarbital. When, however, it was suggested that the opening of the pyrimidine ring also occurred, labeling in the 5 position (5-^{14}C-phenobarbital) gave products identical to those obtained from the 2-^{14}C radioisomer, precluding any significant contribution of other metabolic routes (229). Thus, not only should that position be labeled that is easiest from the synthetic point of view, but so should any others that will provide significant information.

An elegant technique has been developed by Lissitzky *et al.* (230) for the study of thyroid function and the action of several pharmacological agents on thyroid processes. Pregnant rats were fed on a ^{127}I free diet, (*e.g.*, Remington), and given ^{125}I as the single iodine source. After birth, the young rats were kept on this same diet, so that their thyroid had only ^{125}I. When dynamic studies were conducted, ^{131}I was used, allowing a clearer understanding of the pharmacological action of goitrogenic agents. Such studies illustrate the potential of the simultaneous use of several isotopes of the same element (115).

Another aspect is illustrated by the work of Buyske and co-workers (231) on the agents affecting the activity of tetracycline. Tritium-labeled tetracycline was used, by an isotope dilution technique, for the determination of tetracycline levels in blood. Other labeled materials could be rapidly screened as synergistic agents, and this led to an understanding of the interaction of calcium salts with tetracycline.

Body distribution of drugs is of the utmost importance. Several techniques have been developed recently, based on autoradiographic methods, for determining drug distribution and localization. They involved administration of the labeled drug to an animal, which is then sacrificed by freezing at $-80°$, and sections are prepared at $-10°$ (232) or at $-60°$ (233) followed by autoradiography of the dried sections. The results of such methods of cellular localization are only now beginning to emerge, and will certainly constitute an important tool in the determination of the mechanisms of drug action.

Roth *et al.* (234) have studied the entry of drugs into the brain in an attempt to understand the factors that influence and control the barrier function that restricts the entry of substances into the central nervous system. Among the drugs studied were acetazolamide, thiopental, diphenylhydantoin, and pyridine 2-aldoxime methiodide (2-PAM). These authors observed that the blood-brain barrier could be altered by the percentage of CO_2 in plasma, convulsions, and sensory stimulation, thus suggesting that proper manipulation of such factors may allow a directive effect in brain localization.

An intriguing tool is that of the deuterium isotope effect. Deuterium is an isotope of hydrogen with a mass of 2. Differences in reaction rates have been observed between H- and D-labeled compounds. When there is a transfer of the isotopic atom from the reactant to an acceptor, a primary isotope effect ($k_H/k_D = 1.5$ to 10.0) can be observed. A further isotope effect (secondary) is observed when no transfer occurs, but the isotope is strongly involved in the interaction with the active site of the enzyme ($k_H/k_D = 1.05$ to 1.30). The significance of such isotope effects has been studied by several authors. Thus, the flavoprotein nature of the monoamine oxidase system was demonstrated by Belleau (235), while the nature of the interaction between morphine and its receptor site was studied with the aid of *N*-deuteromethyl morphine by Elison *et al.* (236).

A variety of methods have been developed specifically for the synthesis of labeled radiopharmaceuticals. Stepka and Larson (237) isolated nicotine, digitoxin, and ephedrine, among others, from higher plants grown in an atmosphere enriched with $^{14}CO_2$. Chemical syntheses have been widely reviewed, and the reader is especially referred to excellent papers by Rothchild (238) and Bayly (101, 239) as well as to reviews previously mentioned (88, 91, 102, 103).

While both pharmacologists and biochemists have been making excellent use of radionuclides in the understanding of physiological, pharmacological, and pathological processes, the same cannot be said for those in nuclear medicine. As Bayly points out (101), only a few radiopharmaceuticals currently in use as diagnostic agents are true "biochemicals," while all others are either inorganic salts or tagged polymers. The need for designing new radiopharmaceuticals, based on the principles so successfully applied to experimental pharmacology and biochemistry, is great, and Wagner (240) has analyzed the characteristics of an ideal radiopharmaceutical, which should guide research in the development of new agents of this type.

USE OF RADIONUCLIDES AND RADIATION PROCEDURES IN THE PHARMACEUTICAL INDUSTRY

Since the last excellent review of the applications of radionuclides and radiation in the pharmaceutical industry (241) only a limited number

of reports have appeared concerning application of radioisotope techniques to the pharmaceutical industry.

This review will present and correlate these reports and will show some diversified applications. It is sincerely hoped that pharmaceutical scientists will acquire proficiency in the techniques of radioisotope methodology and adapt this unique tool to the pharmaceutical industry.

The system of quality control, pyrogen testing, and sterility control in operation in a large clinical center laboratory for the preparation of radiopharmaceuticals is well described by Briner (104, 211). The recommendations he makes are equally applicable to smaller nuclear-medical and radiopharmaceutical installations.

A patent was issued for a capsule for radioactive pharmaceuticals consisting of a nontoxic water-soluble material and containing a solid material that melts at body temperature. The material is compounded from a pharmaceutically acceptable oil and contains the radioactive product (242). The thickness of the wall of hard gelatin capsules is determined by measuring through the capsule wall the attenuation of the β radiation of a ^{36}Cl source on the tip of the steel dipping pin. A change of 0.0001 in. in thickness was detectable by a change in the counting rate (243).

The moisture content of rubber stoppers and aluminum ferrules used for packaging biological products was determined by measuring retained tritiated water (244).

The determination of moisture content of calcium carbonate, which should be equally applicable to other pharmaceutical materials, was determined by measuring the transmission of β particles from a ^{90}Sr source (245).

A radioisotopic method for evaluating dispersed systems such as liquid petrolatum emulsions for uniformity has been developed (246). The radioisotopic method was much faster for determining the phase uniformity of emulsions and for expressing ratios of creaming, than any other method used.

The determination of rates of settling of suspensions was determined by measuring the characteristic irradiation from a sealed β source. The source was immersed and the attentuation of the beam which passed through a vertical column of the suspension was measured. This method was suggested for determining the sedimentation rate of pharmaceutical suspensions containing elements of high atomic number (247).

Several contributions have referred to the use of activation analysis for the quantitation of trace quantities of metals and other materials used in pharmaceuticals (56–61).

The status of radiation sterilization of pharmaceuticals and medical supplies has not altered significantly since the last general reviews were presented in 1960 (7, 241).

These processes of sterilization are based on the lethal effects of high energy ionizing radiation on living organisms. The radiation may be very high energy electron beams produced in a linear accelerator, or γ radiation produced by a large ^{60}Co source.

The advantages of this type of sterilization are: (*a*) the product may be prepackaged in nonsterile materials in a nonsterile atmosphere and then the product and packaging sterilized; (*b*) it permits greater latitude in the choice of packaging materials; (*c*) bulk materials and products difficult to sterilize by either moist or dry heat can be sterilized; and (*d*) the processes can be made continuous, requiring only small numbers of personnel.

Certain disadvantages are: (*a*) the cost of sterilization is higher than that of heat sterilization and the initial cost of the installation is very high, although this might be offset somewhat by the savings of the cost of operation; (*b*) many materials are damaged by the radiation, suffering changes in color, decomposition, loss of potency, and in some cases, complete impairment of their therapeutic properties.

However, research in the methodology continues, and the following reports have appeared in the recent literature.

Antibiotics and hormones were irradiated in sealed containers by exposure to 10^6 reps without physical damage or loss of biological activity (248). Toxins and enzymes were sterilized with 5 million reps, based on a lethal dose for bacteria of 1 to 4 million reps (248). The rep, now an obsolete unit of absorbed ionizing radiation, was defined as an absorption of 93 ergs of radiation per gram of matter. It has been replaced by the rad, which is equivalent to the absorption of 100 ergs of radiation per gram of matter.

It is, however, generally believed that the lethal dose for bacteria varies from 0.1 to 2.5 megarads (1 megarad = 1 million rads) (249), and the latter figure is presently generally accepted as being safe. In Poland, drugs in ampuls were sterilized by exposure to rays from a ^{60}Co source. The enzyme cocarboxylase hydrochloride in dry form, contaminated with spores of *C. welchii*, *C. septicum*, and *E. coli* was sterilized with 4×10^5 reps from ^{60}Co. The material was sterile and showed no signs of decomposition. In aqueous solutions nonsporulating *E. coli* required 8×10^5

reps, while *C. welchii* and *C. septicum* required 1.6×10^6 reps (250).

Ophthalmic ointments containing oxytetracycline, chlortetracycline, tetracycline, and polymyxin in petrolatum and lanolin were sterilized and could be treated so in aluminum tubes and packaged. The dose was 2 million rads (2 Mrad) from a ^{60}Co source (251). The pH decreased slightly but the chemical composition and biological activity were unchanged, and the ointment was stable at room temperature for 14 months.

Ophthalmic ointments containing penicillin and fluorescein were sterilized by a dose of 2.5 Mrad from a γ ray source in their final containers and packages (252).

Antibiotics, anticoagulants, hormones, plasma, multivitamin preparations, and steroids were sterilized with 2 Mrads. The importance of preconditioning the containers was emphasized (253).

A report of 7 years' experience with radiation sterilization was presented (254). The types of products, the materials used, as well as certain aspects of processing and control and a comparison of irradiators, were given.

Recent developments in Sweden were reported (255). The following radiation sources have been used: β radiation, γ radiation from ^{60}Co and from spent fuel elements from reactors, megavoltage from Van De Graaff generators, and from linear accelators. The dose of 2.5 Mrad is equivalent to autoclaving at 120°/20 min. Unfortunately, many pharmaceuticals discolor and develop off-odors and decrease in potency. Glass is also discolored. γ Radiation does not seem too favorable. The area of greatest application is for disposable medical supplies such as adhesive, dressings, catheters, and especially plastic syringes and other items for single use. However, the cost is high. A novel suggestion is the addition of radionuclides of short half-life to injectables for self-sterilization, an idea fraught with legal complications.

A recent monograph reviews sterilization and disinfection as applied in medical, industrial, and laboratory practice, using ionizing and nonionizing radiation (256). A related application of γ radiation is its use in the preparation of noninfective antigens for the laboratory diagnosis of virus diseases such as influenza, mumps, herpes, and small pox (249). These antigens are commonly prepared in a stable, noninfective form using formaldehyde, but the infectivity of soluble antigens cannot be destroyed in this manner. γ Radiation offers an alternative way and appears to be superior for the preparation of the herpes simplex antigens.

The preparation of vaccines using γ radiation instead of formaldehyde is under investigation, and this technique shows promise (249).

Cold sterilization using linear accelerators has been used successfully for surgical sutures for many years.

Active research and development will undoubtedly show that many pharmaceuticals and medical supplies can be sterilized by radiation suitably and economically to compete with present day methods.

CONCLUSIONS

The authors have attempted to present here an overview of the present status of radiopharmaceuticals, the methods for detecting them, some of the advances in new short-lived radionuclides, and some directly related subjects.

If we would like to characterize developments in recent years, one single term would suffice to describe it: sophistication. Thus, newer, better, complex, and very reliable instrumentation has been developed for the detection both *in vitro* and *in vivo* of radionuclides, thanks in part to the notable developments in solid-state electronics. The ability of the A.E.C. sponsored national laboratories (Brookhaven, Argonne, Oak Ridge) to produce any desired radionuclide and of the nuclear industry to make these available at reasonable cost to investigators in the health sciences, has further widened the horizons of radiopharmaceuticals. The example of ^{99m}Te, a radionuclide with a half-life of 6 hr., is indicative of the present trend toward radionuclides with a shorter half-life involving much less exposure of the patient to radiation. *In vitro* testing of biological functions such as the various methods available for protein bound thyroid hormone based on the original work by Hamolsky in 1957 illustrates another trend: that of using radionuclides in the clinical lab without any exposure to the patient. A third development, only beginning, is that of the use of tritium and ^{14}C-labeled biochemicals for measurement of specific metabolic disorders.

The rationale for present and future developments is given by work in biochemistry and in experimental pharmacology where radionuclides constitute a self-evident and most significative tool.

The authors feel that radiopharmaceuticals are a rapidly growing field with a tremendous potential which has not been fully explored. Especially, new radiopharmaceuticals are required, more

directly based on metabolic functions and designed by applying biochemical and pharmacological principles. This challenge stands before the pharmaceutical sciences.

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