RECENT DEVELOPMENTS IN ISOTOPE PRODUCTION AND SOURCE FABRICATION*

by

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Tremendous strides have taken place in the past decade in man's capacity to make radioactive atoms. The number of known kinds of manmade atoms is now close to one thousand. Radium 226, the isotope of radium whose medical use generated this Society, is now just one of hundreds of useful radioactive species. The total activity of radioactive materials produced by nuclear chain reactions, both controlled and uncontrolled, staggers the imagination. The energies and beam intensities of nuclear particle accelerators have increased a thousandfold and more. Thus, man is now in the fortunate technical position of being able to develop production of any desired radioisotope in sufficient amount and purity to meet all demonstrated needs.

Physicians and medical research workers are already making good use of those isotopes that have become readily available.[1] Of the potentially available radioisotopes, however, only a dozen or so are used routinely in diagnosis and therapy, and fewer than 100 in medical research. Progress in radiation instrumentation, isotope scanning techniques, whole body counting, in vitro diagnosis and combined radiation-chemotherapy will

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DISTRIBUTION OF REACTOR RADIOISOTOPES
FROM OAK RIDGE NATIONAL LABORATORY
August 2,1946 - March 1,1962

TABLE Ia - Items Totaling Over 1000 Curies

Isotope	Shipments	Curies
Cesium 137	1,792	222,533
Cobalt 60	2,755	1,058,869
Gold 198	743	1,019
Hydrogen 3	1,379	150,293
Iodine 131	48,805	7,324
Iridium 192	992	47,187
Krypton 85	608	15,063
Phosphorus 32	31,030	1,962
Promethium 147	509	4,893
Strontium 90	990	100,408
Total	89,603	1,609,551

TABLE Ib - Items Totaling Less Than 1000 Curies

Isotope	Shipments	Curies
Calcium 45	2,905	36
Calcium 47*	331	0.4
Carbon 14	4,139	156
Chromium 51	1,669	83
Iodine 125**	76	1
Iron 59	2,965	10
Potassium 42	3,311	54
Sodium 24	2,818	22
Strontium 89	1,178	61
Sulfur 35	4,916	183
Xenon 133	25	648
Others (~70 radioisotopes)	45,254	1,824
Total	69,587	3,078
GRAND TOTAL	159,190	1,612,629

* Distributed only since October 1961
** Distributed only since July 1960

$$A(t) = P\left[1 - e^{-\frac{0.693}{T_{\frac{1}{2}}}t}\right]$$

where $A(t)$ is the activity produced as a function of exposure time t, $T_{\frac{1}{2}}$ is the half life of the radioisotope produced, and P is the rate of production. P is directly proportional to the neutron flux and the nuclear transformation characteristics of the target material; i. e., the cross section for the production process of interest as well as for competing reactions. For an infinitely long exposure and a constant amount of target material, a certain maximum activity would be reached where production is equal to radioactive decay. For practical purposes irradiations are seldom conducted for more than three half lifes.

This simple expression for radioisotope production is complicated by several factors: a number of nuclear reactions may be occurring simultaneously, a significant amount of the target may be used up in long irradiations, and the desired product may itself undergo nuclear reactions.

If the radioactive product has a high cross section for neutron capture, it will be "burned up" in long exposures. Burnup may be undesirable not only because of loss of the valuable material but also because the isotope produced by the sequence of neutron absorptions may itself be radioactive and have undesirable radiation characteristics. In such a case, a brief irradiation in an intense flux is desirable to avoid the production of significant quantities of the unwanted radioactive contaminant. Prompt removal of the desired radioisotope also may be needed to avoid burnup or to minimize secondary reactions leading to radiochemical impurities.

simply to greater specific activities. Although cobalt 60 itself has a moderate cross section for neutron absorption, thus forming cobalt 61, radiation contamination is avoided because of the short 1.65-hour half life of the latter, which decays to a stable nickel isotope. The quantity of nickel produced is usually so minute that it does not represent a significant impurity nor does it reduce the activity of a given source to a serious extent.

If the target element consists of a mixture of stable isotopes, several concurrent nuclear reactions may go on, leading to a mixture of radioisotopes of the same element that are not separable by chemical means. In some cases, however, the product isotopes differ so greatly in decay rates that a feasibly short storage time will result in material consisting principally of the longer-lived radioisotope. In other cases it may be essential to separate the stable isotopes before using them as target material.

One of the most important factors in the production of isotopically and radiochemically pure materials has been the increased availability of higher neutron fluxes. Before the advent of intense neutron fluxes, it was necessary to resort to transmutation, fission, or Szilard-Chalmers reactions with subsequent complicated chemical isolation procedures to obtain radioisotopes of high specific activity. With several reactors available for isotope production with neutron fluxes of 10^{14} neutrons/cm^2/sec or greater (Table II), satisfactory material can now be obtained in many cases by simple neutron capture reactions. Further increases in flux to

the 10^{15}n/cm^2/sec region as in the new High Flux Isotope Reactor (HFIR) under construction at Oak Ridge will extend this trend.

Scheduled for completion in 1964, the HFIR is intended primarily as a production facility for gram quantities of californium and other transplutonium elements, but it will also have space for production of useful medical isotopes. Its flux of 3-to-5 x 10^{15}n/cm^2/sec will be the world's most intense neutron flux. This will permit production of radioisotopes with specific activities over 1000 times greater than with the original X-10 graphite reactor.

Almost all radioisotope production would be benefited by having higher-flux reactors available. In particular, much higher specific activities of short-lived isotopes could be produced -- unless burnup of the desired product is a factor. The short half life makes it practical to go essentially to "saturation," where the rate of production is equal to the rate of decay. Saturation is the theoretical maximum production and in all cases is directly proportional to flux. An example of the advantage of high flux from Table III is in the production of sodium 24, which has a 15-hour half life and a very low cross section for neutron absorption. The ten-times-higher flux gives material having ten times the activity per gram of starting material.

On the other hand, a high flux is of less advantage when the short-lived product has a high cross section for neutron absorption. In this case, maximum production is much below the saturation value. Gold 198 is an example. As shown in Table III, it has a high cross section for

burnup of 26,000 barns. Less than twice the activity per gram of starting material can be obtained in this case for a ten-fold increase in flux.

With high fluxes, reactor irradiation could be continued beyond the point of maximum production in order to burn up more target atoms. This has the effect of increasing the true specific activity (curies of desired isotope per gram of its element). At the same time, if the cross section of the product is comparable to or higher than that of the target, burnup of the product introduces other elements by transmutation reactions. Therefore, to take full advantage of the increase in specific activity through target burnup, it is necessary to chemically separate the desired product element. In the case of cobalt 60, for example, it should be possible by very intense neutron irradiation of cobalt 59, followed by chemical separation of the transmutation product nickel, to closely achieve the theoretical specific activity of 1140 curies per gram. For short lived isotopes such as sodium 24, however, the theoretical specific activities are so enormous that attaining them would be impractical by this method even if desired.

A significant advantage of high-flux reactors is the possibility of producing high-specific-activity material by (n, γ) reactions that must now be made by neutron transmutation of another element, with subsequent expensive chemical separation. Phosphorus 32, for example, which is made by neutron bombardment of sulfur, could be made directly from a stable phosphorus 31 target. With a 10^{15} neutron/cm^2/sec flux, activities of more than 100 curies per gram could be obtained by this route at a greatly reduced cost.

electromagnetic separators. As a result, the ratio of activities of a desired radioisotope to unwanted radioisotopes may be raised to almost any desired value. Oak Ridge National Laboratory began its electromagnetic separation program over 15 years ago with the enrichment of two stable isotopes of copper. The program now covers all the known stable isotopes -- more than 250 -- are now routinely available in enriched form.

Examples of better and less expensive radioisotope preparations produced from enriched isotopes are chromium 51, from enriched chromium 50; iron 59, from enriched iron 58; and calcium 47, from enriched calcium 46. Calcium 47 is particularly interesting because there has long been a need for a gamma emitting isotope of calcium. Calcium 47 is such an isotope but is also an example of a difficult material to prepare without isotopic enrichment of the target. The natural abundance of calcium 46 is only 0.0033%; thus one kilogram of natural calcium must be put through an electromagnetic separator to collect only 6 milligrams of calcium 46. Since the product material still contains some calcium 44, the reactor irradiation produces calcium 47 contaminated with calcium 45. The activity of calcium 47 available on a routine basis has been raised to a Ca^{47}/Ca^{45} ratio of 40:1 (when shipped).

As a result of the use of enriched isotopes, much higher specific activities of the most useful isotopes can be produced in a given reactor (Table IV).

Fission Products

Fission of reactor fuels leads to an intensely radioactive mixture of approximately 200 radioactive species. The half lives of the fission fragments range from microseconds to millions of years. Included are such medically important radioisotopes as iodine 131, strontium 90, cesium 137 and krypton 85. Iodine 131 is currently made at Oak Ridge National Laboratory by neutron fission of highly enriched uranium 235. This is a economical process but not suitable for production by private industry. because other fission products are produced and must be handled. Iodine 131 made commercially is produced by the reactor irradiation of tellurium.

The great quantities of radioactive wastes produced when reactor fuel elements are processed to recover unreacted uranium have long been recognized as valuable reservoirs of long-lived fission products, such as strontium 90, cesium 137 and cerium 144, for use in medical therapy, isotopic power generators and heat sources.

A milestone in making available very large quantities of fission products, such as cesium 137, was the completion of the Fission Product Development Laboratory at Oak Ridge National Laboratory. This facility makes possible separation and purification of kilocurie to megacurie amounts of the important long-lived fission products.

For teletherapy purposes, the advantages of having cesium 137 as free as possible of cesium 134 contaminant are well recognized. Changes in radiation output with a mixed source are significant over a fairly short time since cesium 134 decays with a 2.3 year half life, while cesium

simplicity of cesium 137 separation and preparation for shipment indicates that massive quantities of the material can be made available at reasonable cost.

Accelerator-Produced Radioisotopes

Throughout the period 1934-1945, most radioisotopes used were produced in cyclotrons[7]. Today, the cyclotron complements rather than competes with the nuclear reactor for production of radioisotopes. The cyclotron is an important source of certain medically useful isotopes that cannot be produced in a reactor. Cyclotron-produced isotopes frequently are those that lie on the neutron-deficient side of the nuclear stability line. These decay principally by positron emission or orbital electron capture.

Cyclotron-produced radioisotopes, in general, have a distinct advantage of high specific activity since they ordinarily are isotopes of a different chemical element than the target and hence can be chemically separated in carrier-free form.

While numerous cyclotrons in the United States produce radioisotopes to a certain extent, the principal source of those made available commercially is the unique high-beam-intensity 86-inch cyclotron at Oak Ridge National Laboratory.[8]

The construction of the 86-inch cyclotron is novel in that it is a vertical cyclotron in which the dees hang suspended between the poles of a 400-ton magnet. It is otherwise a conventional fixed-frequency machine which produces protons with energies up to 23 Mev. The important feature is that high beam currents of 1 to 2.6 milliamperes can be routinely

TABLE V

SOME RADIOISOTOPES ROUTINELY PRODUCED
BY OAK RIDGE NATIONAL LABORATORY 86-INCH CYCLOTRON[9]

Isotope	Half-Life	Radiations *
Beryllium 7	53.6 day	EC, γ
Sodium 22	2.6 yr	β^+, EC, γ
Vanadium 48	16.1 day	β^+, EC, γ
Manganese 52	5.5 day	β^+, EC, γ
Iron 55	2.9 yr	EC
Cobalt 56	77.0 day	β^+, EC, γ
Cobalt 57	270.0 day	EC,
Cobalt 61	1.65 hr	β, γ
Arsenic 74	17.5 day	β^+, EC, β, γ
Strontium 85	65.0 day	EC
Yttrium 87, 88	105.0 day	EC, γ
Yttrium 88	105.0 day	EC, γ
Technetium 95	20.0 hr	EC, γ
Rhodium 102	210.0 day	β^+, β, γ
Palladium 103	17.0 day	EC, γ
Cadmium 109	1.3 yr	EC
Iodine 124	4.2 day	β^+, EC, γ, β
Barium 133	7.2 yr	EC, γ
Cerium 139	140.0 day	EC
Promethium 145	18.0 yr	EC, γ
Promethium 148	42.0 day	β, γ
Promethium 150	2.7 hr	β, γ
Europium 146	4.4 day	β^+, EC, γ
Europium 147	24.0 day	EC, γ
Europium 149	120.0 day	γ
Gold 195	185.0 day	EC, γ
Thallium 202	12.0 day	EC, γ
Bismuth 207	28.0 yr	EC, γ

EC, electron capture

* Energy values may be found in various nuclear data tables, which are conveniently listed in reference 10.

certain advantages or unique applications that make it worthwhile to consider their availability and potentialities as a group. Similarly, low energy radiation emitters or positron emitters may be considered as groups. Awareness of production progress in such special categories of radioisotopes may lead to employing them in broader applications.

Short-Lived Isotopes

Short-lived isotopes have significant medical advantages: (1) Larger quantities of activity can be administered to patients to obtain a higher response, yet the total exposure may be considerably reduced; (2) Tests may be repeated frequently; (3) Costs of waste disposal and problems of contamination are greatly reduced or eliminated.

Moderately short-lived isotopes (several hours to several days) are produced by reactors or accelerators with no particular difficulty except the need for faster chemical processing and utilization of air transportation. Almost any point in the United States is less than a day's distance by air freight, thus a great variety of short-lived radioisotopes can be shipped and used successfully. Table VI lists some moderately short-lived reactor-produced, regularly available radioisotopes.

The use of short-lived isotopes in the medical field can be greatly extended by making them available in the user's laboratory. A considerable number of small research and isotope production reactors are now available in universities and research laboratories throughout the United States and other countries. This should permit more attention to local use of short-lived isotopes.

A special way of achieving local availability is to milk a short-lived daughter activity from a longer-lived parent, in a fashion similar to the classical milking of radon from radium.

There are some two dozen pairs of parent-daughter related isotopes, where the daughter's half life is shorter than that of the parent and the relative half lives make a milking system feasible. A few of these for which practical radioactive "cows" have been made are listed in Table VII. Three of these radioactive cows are routinely available from Brookhaven National Laboratory: iodine 132, technetium 99m, and yttrium 90.[11]

TABLE VII

SOME RADIOACTIVE "COWS"

Isotope Product (Daughter)	Half Life	Radiations	Parent	Half Life	Ref.
Barium 137	2.6 min	β	Cesium 137	30 yr	1
Gallium 68	58 min	β, γ	Germanium 68	290 days	2
Indium 113m	1.73 hr	IC, γ	Tin 113	118 days	3
Iodine 132	2.3 hr	β, γ	Tellurium 132	77 hr	4
Technetium 99m	6.0 hr	γ	Molybdenum 99	67 hr	4
Yttrium 90	64 hr	β	Strontium 90	28 yr	4
Strontium 87m	2.8 hr	γ	Yttrium 87	80 hr	5

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2. Gleason, G. I. Intern. J. Appl. Radiation and Isotopes, 1960, 8, 90.
3. Meyer, W. J., and Anderson, R. L. Ind. Eng. Chem., 1960, 993-4 (Dec.).
4. Reference 11, this paper.
5. Myers, W. G. J. Nuclear Med., 1960, 1, 125, (Apr.).

To obtain iodine 132 and technetium 99m, the parent tellurium and molybdenum activities are produced as fission products and are separated carrier-free from reactor-irradiated uranium. The parent materials are

having no gamma radiation. Its beta radiation, with a maximum energy of 2.26 Mev, is higher than that of either gold 198 or phosphorus 32 and therefore penetrates more deeply in the tissue. The half life of 2.7 days is considerably shorter than that of 14.3-day phosphorus 32. About 5000 millicuries of yttrium 90 can be milked from a 100-millicurie strontium 90 generator in one year, hence it is potentially one of the cheapest radioisotopes available.

Brookhaven National Laboratory also makes available two short-lived isotopes, magnesium 28 and fluorine 18, of particular interest becuase they are produced by triton reactions in a nuclear reactor. Both can be cyclotron produced, but reactor production is advantageous when quantity production and low price are considerations.

Magnesium 28 (21.4 hour half life) is produced by the $Mg^{26}(t,p)Mg^{28}$ reaction using tritons generated by the reaction $Li^{6}(n,t)He^{4}$. The target material is an alloy of 75% lithium 6 and 25% magnesium by weight. At a thermal neutron flux of approximately 1×10^{13}, specific activities ranging from 1 to 2 millicuries of magnesium 28 per gram of stable magnesium are produced by this method.

Fluorine 18 (112 minute half life) is produced in a reactor by the reaction $O^{16}(t,n)F^{18}$ using tritons from the $Li^{6}(n,t)He^{4}$ reaction. It decays by positron emission and has the characteristic annihilation gamma rays associated with it. Although the fluorine 18 half life is short, it is the only isotope of fluorine sufficiently long lived to serve as a tracer. It may also find application in localization work using the annihilation gamma scanning technique.

Low Energy Gamma and X Ray Emitting Isotopes

Radioisotopes that emit only one type or energy of radiation permit specific applications without complicating side effects. Thus, isotopes that emit only low-energy gamma or x rays have special advantages for diagnosis or therapy, while giving little radiation dose to surrounding healthy tissue and reducing the radiation hazard to operating personnel.

An example of a low energy emitter is palladium 103 which has been used for internal tumor therapy at the Argonne National Laboratory in a number of patients. Some substantial palliation resulted with no serious complications. Palladium 103 emits 20 kev x rays and has a 17-day half life. In contrast to higher energy gamma emitters, it is easy to work with since a cumbersome lead syringe to protect the surgeon's hands is not necessary. The palladium is injected as palladium black in particles of 100 to 500 microns. Being highly insoluble and chemically inert, these do not migrate from the tumor site.

Palladium 103 has been obtained by reactor bombardment of palladium metal. Unfortunately, only low-specific-activity material containing radiation impurities such as neutron-activated iridium is obtained by this method.[13] The precursor palladium 102 has a natural abundance of only 1%. The material can be produced carrier-free in curie quantities by proton bombardment of rhodium, as has been demonstrated with the ORNL 86-inch cyclotron.

Iodine is an excellent example of an element having a wide variety of useful radioisotopes. Of the 20 known radioisotopes, iodine 131 has

TABLE VIII

SOME LOW ENERGY PHOTON EMITTERS
SUITABLE FOR RADIOGRAPHY

Isotope	Half Life, Days	Principal Energies, Kev
Gadolinium 153	236	42, 70, 97
Iodine 125	60	35
Palladium 103	17	40
Promethium 147	920	*
Samarium 145	360	39, 61
Thulium 170	127	52, 84**
Ytterbium 169	32	110, 130, 198

* Bremsstrahlung from 223 kev beta particles.
** Plus bremsstrahlung from 970 and 886 kev beta particles.

New Methods of Isotope Labeling

Diagnostic and research applications of radioisotopes require that numerous complex organic compounds be labeled in various positions with radioactive isotopes. The preparation and distribution of labeled compounds and radiopharmaceuticals has for many years been a commercial business. There are dozens of companies bringing out new labeled compounds. The ability to prepare useful radiomaterials often depends on starting with elemental radioisotopes having high specific activities, as produced through Commission development and production activities.

Tritium-labeled materials, while little used except in research, have possibilities for both diagnosis and therapy. The short range beta particles localize radiation effects in regions as small as cell nuclei.

One of the most valuable and commonly used labeling techniques is the Wilzbach self-labeling method, in which organic compounds are simply exposed to large quantities of gaseous tritium.[18,19,20] Modifications

Source Fabrication and Safety Evaluation

Sealed radiation sources, hundreds of which are employed in U. S. hospitals for interstitial or teletherapy use, are continually being improved in regard to safety and utility. Leak proofness has been increased through new methods of encapsulation, while assurance against damage in fires or accidents has been accomplished through improved containment and shielding.

Cobalt 60 for teletherapy is employed in metallic form, usually nickel plated against corrosion, then double encapsulated by welding in stainless steel capsules. Cobalt 60 used in brachytherapy radiation sources may be in the form of metallic cobalt wire, bare or nickel plated, or wire made from a cobalt-nickel alloy (Cobium). The cobalt wire may be encapsulated in stainless steel and sealed by Heliarc welding, or in platinum-iridium tubes or needles, which are sealed with a brazed or soldered plug. The cobalt-nickel alloy wires are generally encapsulated in stainless steel tubes or needles sealed with a small screw plug.

Cesium 137 in present teletherapy sources most commonly occurs in the form of compacted cesium chloride, double encapsulated in stainless steel or Monel. Although cesium chloride is soluble, it does not attack these metals and has the advantage of compactness relative to other cesium compounds.

Beta ray applicators employ strontium 90 which is incorporated in a ceramic or metal matrix, then doubly encapsulated in stainless steel and

Commission has undertaken a program to develop standard safety criteria for a wide range of sealed sources.[23,24] Current source compositions, designs and fabrication technqiues have been surveyed to evaluate source performance under a wide variety of conditions -- thermal, mechanical, chemical, radiation and pneumatic -- which might be encountered under both normal and abnormal conditions of use. The resulting data will help to accelerate the safe use of radioisotopes by (1) providing regulatory groups with technical guidance in establishing safe and practical regulatory practices and (2) giving manufacturers definite test goals to meet.

Isotopes Development Center

Recognition of the vast potential benefits that will accrue from creative research and development on production and use of radioisotopes has led the Commission to establish an Isotopes Development Center, which is located at its Oak Ridge National Laboratory. Broadened programs of basic and advanced research in isotope technology will be conducted at the Center, which will serve as a focal point for isotope research and development. The Center plans to provide technological data to government agencies, private research groups, industry and educators to assist in expanding beneficial radioisotope applications.

The Center will embrace a complex of radioisotope facilities. It will incorporate the Fission Product Development Laboratory, which develops new methods of separating, purifying and fabricating massive quantities of fission products. Chemical operations on highly concen-

Nevertheless, opportunities are still expanding. With the increased incentives created by advancing medical needs, progress will be accelerated in the production of isotopes and labeled materials. Concurrently, the almost unlimited possibilities for unique isotopic materials will stimulate creative thought toward developing new and wider usage.

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