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SEPARATED ISOTOPES: VITAL TOOLS FOR SCIENCE AND MEDICINE

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Subcommittee on Nuclear and Radiochemistry
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FOREWORD

Washington D.C.
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This report summarizes the deliberations and conclusions of a Workshop on Stable Isotopes and Derived Radioisotopes organized by the Subcommittee on Nuclear and Radiochemistry of the National Research Council's Committee on Chemical Sciences at the request of the Department of Energy (DOE). The workshop was jointly supported by the National Institutes of Health and DOE's Office of Basic Energy Sciences.

An Overview with three recommendations resulting from the Workshop, prepared by the Steering Committee, is followed by Chapters 1 to 4, reports of the four Workshop panels.

Background papers were prepared by individuals on the Steering Committee and made available to all participants prior to the Workshop. They proved of great value and are reproduced as Appendixes 3 to 8. Short reports on alternate separation techniques were presented at the Workshop and are reproduced in Appendixes 9 to 11.

We are deeply grateful to all Workshop participants and especially to the members of the Steering Committee for their contributions. The very efficient staff support of Dr. William Spindel, Mrs. Peggy J. Posey, Mrs. Jean E. Yates, and Mrs. Wendy L. Baker before, during, and after the Workshop are gratefully acknowledged.

Gerhart Friedlander
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OVERVIEW AND RECOMMENDATIONS

The Calutrons at Oak Ridge National Laboratory (ORNL), originally built to produce enriched ^{235}U during World War II, have been used since 1947 to produce enriched stable isotopes for a wide variety of applications. Operated first by the Atomic Energy Commission (AEC), then by the Energy Research and Development Administration (ERDA), and now by the Department of Energy (DOE), the Calutron facility has been the major U.S. source of stable isotopes of most elements. These stable isotopes are used both in scientific research and as precursors of the radioactive isotopes used in biomedical research and clinical medicine. The great versatility of the electromagnetic separation method and its ability to respond rapidly to changing demands make it unique as a general technique. Thus the ORNL facility is an invaluable national as well as international resource; the only comparable electromagnetic separation facility is in the USSR.

For a variety of reasons, however, serious shortages of stable isotopes now exist. Some 60 isotopes are currently not available from ORNL, and under the current funding schemes further deterioration of the inventory appears inevitable. This will have serious consequences for many areas of physics, chemistry, biology, and geosciences, where stable isotopes are indispensable tools. Nuclear medicine has developed to the point where further erosion in the supply of stable isotopes could threaten the health of millions of patients.

Recognizing the seriousness of the problem, the Office of Basic Energy Sciences at DOE asked (Appendix 1) the National Research Council to convene a Workshop to assess the needs for stable isotopes in the scientific, medical, and industrial communities. The Workshop was cosponsored by the National Institutes of Health and organized under the aegis of the Subcommittee on Nuclear and Radiochemistry of the NRC Committee on Chemical Sciences. It was held February 2-4, 1982 at the National Academy of Sciences, Washington, D.C. The participants are listed in Appendix 2.

Background papers were prepared by members of the Workshop steering committee and distributed to participants prior to the Workshop. These papers served as important resource documents and were the basis of the initial presentations to a plenary session. They are appended to this report (Appendixes 3-8). Following the plenary session, the participants broke up into panels dealing with the use of isotopes in the following areas: (1) research in physics, chemistry, and the geosciences; (2) research in biology and medicine; (3) clinical applications; and (4) commercial production of radiopharmaceuticals and radiochemicals. The four panels prepared preliminary reports, which were discussed in plenary session and further refined. Considering the diverse professional backgrounds and interests of the participants, the conclusions of the four panels were

remarkably similar. These reports, with the conclusions arrived at by each Panel, form the basis of the Workshop recommendations given below.

All four panels concluded that an adequate supply of a broad range of separated isotopes is vital for their respective disciplines. The deleterious effects of the unavailability of many isotopes was documented, and replenishment of the isotopes not now in stock emerged as a high-priority objective. It was also agreed that mechanisms should be established to ensure a continued supply of stable isotopes for all segments of the user community. The Workshop participants took note of the fact that users not only in the United States but also in the rest of the western world depend on the ORNL Calutrons as their principal source of most stable isotopes. Thus, the worldwide need for stable isotopes, especially in research (which appears to constitute at least twice the amount of isotopes used in U.S. research) should be taken into account in future planning.

More detailed considerations and conclusions appear in the subsequent chapters of this report. The following are the general recommendations that emerged from the Workshop and represent a consensus of the views of the participants.

Recommendation 1: The production rate of the ORNL electromagnetic separation facility should be increased to utilize more fully the existing physical plant. This increase in production should be carried out to replenish, as soon as is practical, the rapidly diminishing supplies in both the Research Materials Collection (RMC) and the Sales Inventory, and subsequently to maintain a complete range of isotopes in both inventories at adequate levels.

Recommendation 2: Mechanisms are needed to ensure adequate supplies and equitable distribution of electromagnetically separated isotopes to all segments of the user community, as well as to avoid violent price fluctuations. To this end, the appointment of an advisory committee responsible to the administrative level in the Department of Energy that has authority for policy in the Stable Isotopes Program is recommended. This committee would advise DOE on overall policy regarding stable isotopes, gather information on anticipated needs, keep informed on production activities, and provide counsel on the allocation of resources between the sales and research inventories.

Recommendation 3: Research and development efforts should be directed toward the demonstration of alternative enrichment technologies which might in the future complement ORNL's electromagnetic separations program for certain isotopes. This recommendation stems from the facts that the degree of enrichment afforded by the electromagnetic technique is significantly greater than required for some applications, and that some alternative technologies now in the research stage may have the potential for achieving adequate enrichment of specific isotopes at lower cost.

1

RESEARCH APPLICATIONS IN PHYSICS, CHEMISTRY, AND GEOSCIENCE

I. INTRODUCTION

In many areas of basic scientific research, the need for enriched stable isotopes is as vital as the need for pure chemicals. Separated isotopes are necessary in many nuclear studies, and they also are required for a wide variety of techniques in other disciplines. The U.S. electromagnetic separation program at Oak Ridge is the sole provider of most such isotopes in the western world and is thus a unique and essential resource.

II. RESEARCH APPLICATIONS

A. Nuclear Physics and Chemistry

A wider spectrum of separated stable isotopes is used in nuclear physics and chemistry research than in any other discipline. During the last few years, more than 75 percent of the 280 nuclides that occur in nature have been used in these fields of research. However, the quantities of isotopes used by individual researchers are small, ranging typically from 10 to 1,000 mg per year. The main reason for the wide use of enriched isotopes is that many important nuclear properties differ, often drastically, from isotope to isotope. In most cases, the use of naturally occurring mixtures of isotopes would confuse or obscure the interpretation of experiments. Since the properties of individual isotopes differ, an understanding of many key aspects of nuclear science depends on systematic studies of nuclei as a function of neutron and proton number. This is true of both nuclear-structure and nuclear-reaction research.

Our understanding of the nucleus, and especially of nuclear structure, is based on measurements of the properties of specific nuclides. Our knowledge of the interplay of the extremes of single-particle and collective models of nuclei comes from tracing the disappearance of shell effects and the onset of deformation in series of isotopes--for example, in calcium nuclei, which stretch from mass 40 to 48, spanning a 40 percent range of neutron-to-proton ratio. In samarium nuclei, which vary in mass number from 144 to 154, a complete evolution from closed-shell to vibrational and then rotational nuclei has been observed. There are many other examples of such systematic studies, dealing with diverse properties such as nuclear radii and pairing correlations.

Modern studies of new collective modes of nuclear vibration, and of changes in the shape of a nucleus under the stress of high angular momentum, have increased the need for a wide range of separated stable isotopes. Virtually all nuclear studies require separated isotopes, since the properties of a nucleus can change drastically with the addition or removal of even a single nucleon.

In the field of nuclear reactions, our ability to vary the ratio of neutrons to protons in projectiles and targets is important in many types of investigations, ranging from the study of the nuclear optical potential to the evolution towards equilibrium of a quantal system composed of various numbers of protons and neutrons.

The above examples demonstrate the importance of the availability of many isotopes with a moderately high enrichment ($\lesssim$95 percent). Other aspects of nuclear physics and chemistry require very high enrichments of the rarest isotopes. Studies of exotic light and medium mass nuclei far from the valley of beta-stability, investigations of the nuclear physics and radiochemistry of transuranium elements, and searches for the elusive superheavy elements must be conducted on targets composed of rare isotopes in which even slight traces of more abundant species can lead to unacceptable backgrounds.

To an increasing degree, extremely neutron-rich and neutron-poor stable isotopes (e.g., ^{36}S, ^{40}Ca, ^{48}Ca, ^{58}Ni) are being used as projectiles to explore the limits of stability of light and medium mass nuclei, as well as to search for superheavy elements. The isotopic material is placed in the ion source of an accelerator, so that a partial enrichment to $\lesssim$50 percent would be acceptable. While the Calutrons at ORNL automatically produce fairly high enrichments of most isotopes, the modest enrichments required for these applications might be achievable at much lower cost by other separation methods. Typical consumption in an ion source ranges from 1 to 50 mg per day (depending on the particular accelerator), allowing for 80 percent recovery.

Although the general trend in nuclear physics and nuclear chemistry research is to use a wide variety of stable isotopes in small amounts, investigators in such fields as electromagnetic interactions, medium energy physics, and neutron physics often make use of larger quantities (tens to hundreds of grams). Many of these uses are non-destructive and can be met by loans of isotopes from the Research Materials Collection. In the future, however, there is likely to be greater emphasis on experiments involving species of lower abundance; for example, in neutron physics research osmium isotopes are of great interest, but they are at present not available in large quantities.

B. Analytical Uses of Separated Isotopes

Separated isotopes have many analytical applications; at the present time their uses are most widespread in mass spectrometry (MS) and nuclear magnetic resonance spectrometry (NMR). The MS uses are largely destructive--i.e., the isotopes are consumed during analysis.

Although the amount of isotope needed for an individual analysis is small, separated isotopes of nearly every polynuclidic element are used. During the past 10 years, while the technique was being developed, the emphasis in mass spectrometry was on the heavy metals (e.g., Cd, Pb) and on certain lighter elements (Mg, Ca) and, in general, the separated isotopes were available in the amounts required. Now, however, the needs in mass spectrometry are for a wider variety of elements, for more than one separated isotope per element (where possible), and for higher enrichments (>99.5 percent). When two or more isotopes are available in high enrichment, the "double spiking" technique can be used to give greater accuracy--an important consideration in the determination of elements at trace levels. The use of isotope dilution mass spectrometry is expanding at the rate of about 15 percent per year. The estimated annual U.S. needs are for 5 to 10 g of some isotopes of all elements, in many cases those of low abundance. Of particular interest are isotopes of the rare earth elements (which are not readily available) and those of clinical as well as general analytical interest--e.g., the isotopes of Mg, Ca, V, Zn, Cd, Sn, and Hg.

Although actinide isotopes are, of course, not "stable," they are separated in Calutrons. It is therefore worth noting that there is also a specific need for several of the actinides in both the nuclear and general analytical communities. The typical annual requirements are for 10 to 100 g of ^{233}U, ^{235}U, ^{238}U, and ^{242}Pu, and 10 to 50 mg of ^{244}Pu and ^{244}Cm.

The need for isotopes to determine the atomic weights of the polynuclidic elements is particularly acute for a number of elements, such as Ti and Ge, whose atomic weights are known only to a few parts in 10^4. At least 1 g of each of two or more isotopes is required for each determination, and such quantities are unavailable at present. The systematic determination of more accurate atomic weights, is thus being delayed now and will have to be abandoned unless the required isotopes become available in the next few years.

Separated stable isotopes are also important to nuclear magnetic resonance spectrometry. Increased sophistication in signal averaging, as well as probe frequency, sample size, and magnet size, have made metal ion NMR studies feasible for elements throughout the periodic table. The advances in coordination chemistry and organometallic chemistry through the use of metal ion NMR (particularly for transition elements) that are likely to occur during the 1980's are expected to be comparable to the exploitation of ^{13}C NMR in the 1970's. The sensitivity of NMR measurements for a given nuclide is related to its isotopic abundance, nuclear spin, nuclear magnetic moment, and atomic magnetic susceptibility. A few grams of isotopically enriched stable nuclides for many elements that have spin 1/2 and that exist as diamagnetic species in chemical compounds are expected to be needed. Of particular interest are ^{53}Cr, ^{57}Fe, ^{61}Ni, ^{105}Pd, ^{123}Te, ^{135}Ba, ^{183}W, and ^{191}Ir.

C. Solid State Physics and Chemistry

Studies in solid state chemistry and physics utilize a wide range of techniques, some of which require electromagnetically separated stable isotopes. Areas of current interest include Mössbauer spectroscopy, perturbed angular correlations, neutron scattering, and gamma-ray scattering.

Of particular importance to Mössbauer spectroscopy are the availability of ^{57}Fe (natural abundance 2.1 percent), especially for the study of biological materials containing iron, the use of high enrichment ^{118}Sn (particularly depleted in ^{119}Sn) as target material for the (n, γ) production of ^{119m}Sn, the availability of ^{129}I ($t_{1/2} = 1.7 \times 10^7 y$) as starting material for the synthesis of absorber compounds, and the availability of pure Te isotopes.

Experiments involving perturbed angular correlations require source materials which cause a minimum of interfering radiation when activated to excited nuclear states. These source materials must therefore be depleted in nuclides whose activation could produce such masking radiations.

In neutron scattering studies the large thermal neutron cross sections for some isotopes of polynuclidic elements (e.g., Cd, Sm, Gd, Eu) can only be avoided by preparing samples from enriched isotopes with low cross sections. Variations in neutron scattering length among isotopes have led to a variety of studies in which contrast is changed by varying the isotopic content. This technique has, for example, been used to study crystallographic phasing and radial distribution functions in amorphous systems.

The new technique of γ-ray scattering requires intense radioactive sources of γ-ray beams. Diffraction studies with 1,000 Ci sources of ^{153}Sm ($t_{1/2} = 46$ h) are being performed, for example, and ^{51}Cr sources (strength ≈ 50 Ci) are used for Compton scattering. Nuclides with short half lives are typically used in these studies, which even extend to inelastic Mössbauer scattering with ^{183}Ta sources and enriched ^{183}W absorbers. For spectroscopy studies at Synchrotrons the use of resonant Mössbauer nuclei to select intense, highly monochromatic beams by means of mirrors or crystal monochromators is being considered; the isotopes ^{57}Fe, ^{119}Sn, ^{125}Te, ^{161}Dy, and ^{183}W are of interest in this application. The majority of these uses were not foreseen even two or three years ago and would not be possible without separated stable isotopes.

Many phenomena examined in solid state chemistry and physics show mass dependence. Examples include the influence of isotopic mass on the critical temperature in superconductivity and on the lattice temperature of molecular solids. Thus, the availability of a pool of separated isotopes is crucial to many in the solid state chemistry and physics community, although specific needs cannot be forecast with any precision.

D. Geoscience

The geoscience community has a continuing need for separated isotopes of the elements traditionally used in geochronology, i.e., U,

Th, Pb, Sr, Rb, and K. This demand will probably remain constant for the next few years. The total U.S. need is about 1-10 g per year for each of these isotopes. Of particular concern at the present time is the unavailability of ^{84}Sr of high isotopic and chemical purity. This material, essential to almost every researcher in geochronology, has been "out of stock" at ORNL for several years.

In addition to separated isotopes of the elements traditionally used, isotopes of other elements have recently become important to geoscientists. Of particular interest now are isotopes of Nd and Sm. High purity separated isotopes (> 99 percent) of these and other polynuclidic rare earths are needed, with requirements on the order of 0.5 to 2 g per year.

Nucleosynthesis problems are attracting increasing interest in the geoscience community as well and require separated isotopes of a growing list of elements. Elements that have been analyzed recently include Mg, Ca, Fe, Cd, and Sn. These investigations require not only high isotopic purity (> 99 percent), but also several nuclides per element; the effects being studied are small ($\approx 1{:}10^4$ to $1{:}10^5$) and the "double spike" technique must be used.

E. Fission and Fusion Reactor Technology

A continuous supply of isotopically enriched samples is needed in order to measure nuclear data important to fission and fusion reactor technology. Four areas of interest are addressed here: structural materials, actinides, fission product nuclei, and nuclear standards.

The most important structural material in both fission and fusion reactors is stainless steel. Hence, the long-term integrity of this material must always be examined. Of special interest are capture cross sections, which play an important role in the neutron economy of the fast breeder reactor. For fusion reactors, all of the charged-particle production cross sections (especially those relating to He production) are of interest because of the high priority given to studies of radiation damage. Neutron inelastic scattering cross sections are also important, since they influence the hardness of the neutron spectrum in a fission reactor.

To determine the performance of fission reactors with high fuel burn-up, both heavy-element ($Z \geq 92$) and fission product capture cross section data must be measured. Several important fission products are available as stable isotopes, and separated isotopes of such heavy elements as U, Pu, Am, and Cm need to be studied.

Activation cross sections are necessary in the fusion reactor program in order to determine the usefulness of activation reactions as flux monitors in the energy range above 10 MeV. Provision of standard nuclear cross section sets, to which other cross sections can be compared, is also necessary.

A full understanding of the nucleonic behavior of a composite element or alloy used in a reactor requires detailed knowledge of the constituent isotopic cross sections. Once these are known, it is possible to predict with some accuracy the behavior of the material in

relation to any specific incident neutron energy distribution. For measurements of neutron capture cross sections, relatively large sample sizes are needed to achieve sufficient accuracy, since the relevant cross sections are small. Samples of at least 10 g are required for total-energy detectors. Similarly, large metal samples (typically in cylindrical form) are most desirable for measurements of scattering cross sections.

Most of these measurements can be made non-destructively, but the appropriate electromagnetically separated isotopes have not been available from the Research Materials Collection at ORNL. This is particularly true for heavy elements ($Z > 92$). Some examples of the materials currently needed for reactor technology include isotopes of structural materials, such as nickel, iron, chromium, titanium, zirconium, niobium, and copper; isotopes of stable fission products, such as silver, palladium, and ruthenium; and isotopes of heavy elements, such as ^{230}Th, $^{235,238}U$, $^{239,240,241,242}Pu$, $^{241,243}Am$, and $^{243,245}Cm$. The required measurements can be found on a list (WRENDA) published by the Nuclear Data Section of the IAEA.

III. CURRENT ISOTOPE USE

The use of electromagnetically separated isotopes in scientific research in the United States remains very extensive. Some 220 different isotopes were used in the fields of physics, chemistry, and geoscience between 1979 and 1981.

There are two types of use, destructive and non-destructive. In destructive uses, which are typical of most of the research areas considered here, the isotopes are consumed or rendered non-recoverable. In a few areas, however, such as electromagnetic interactions, medium energy physics, and neutron physics, there are significant non-destructive uses of large samples (tens to hundreds of grams) of separated isotopes. These needs, which amount to about 150 gram atoms per year of various isotopes, can generally be satisfied with loan samples from the Oak Ridge Research Materials Collection.

Table 1-1 summarizes the consumption of separated stable isotopes in nuclear and medium energy physics, nuclear chemistry, and radiochemistry, along with consumption in several "non-nuclear" areas of chemistry (mass spectrometry, NMR), physics (Mössbauer spectroscopy, perturbed angular correlations, laser spectroscopy), and geoscience (geochronology). (Although some information on actinide isotopes was obtained from our survey and included in Table 1-1, no systematic effort was made to collect such data.) Excluding the light isotopes $^{6,7}Li$ and ^{10}B, the annual rate of consumption from 1979 to 1981 was nine gram atoms per year. If non-destructive uses are included, the usage rate during this period was about 160 gram atoms per year. At current prices, the consumption rate corresponds to an expenditure of roughly $500,000 per year. Table 1-2 lists the 20 isotopes for which the largest expenditures were made during the period in physics,

chemistry, and geoscience. These 20 isotopes accounted for about 70 percent of the total expenditure for separated isotopes during the period in the fields under consideration.

Because of lack of information, it is not possible to make a quantitative statement about worldwide consumption of isotopes produced in the United States, but it has been estimated that the use of such isotopes for research in nuclear physics and chemistry in West Germany, Japan, and England amount to roughly 1.5 to two times the U.S. consumption rate shown in Table 1-1. Thus, we can estimate that the total consumption of separated stable isotopes supplied by Oak Ridge for physical research may be approximately three times the quantities shown in Table 1-1.

It is disturbing to note that 60 of the 240 isotopes in the Oak Ridge Catalog are unavailable at the present time (see Table 1-3). Even more disturbing is Table 1-4, which shows a rapid increase with time in the number of unavailable isotopes. Due to limited production time on the Calutrons, very few depleted isotopes have been replaced over the last three years.

TABLE 1-1. CONSUMPTION OF ISOTOPES IN THE UNITED STATES IN PHYSICS, CHEMISTRY, AND GEOSCIENCE[a] (1979-1981)

	No. of Species	Gram Atoms	Approximate Cost
Nuclear Physics/Chemistry & Medium Energy Physics	200	19(475)[b]	$780K
Radiochemistry	53	0.4	$400K
Other Chemistry	26	5.2	$ 35K
Other Physics	47	1.3	$270K
Geosciences	87	0.1	$ 90K
Total (1979-1981)	220	26(482)[b]	$1,575K
Annual Average		9(161)[b]	525K

[a]Excluding $^{6,7}Li$, and ^{10}B. An additional 2,300 gram atoms of these isotopes were consumed during this period, at a cost of about $70,000.

[b]The figures in parentheses include "non-destructive" uses, which can be handled by loans from the Research Materials Collection.

TABLE 1-2. EXPENDITURES FOR MAJOR ISOTOPES USED IN PHYSICAL RESEARCH[a] (1979-81)

Rank	Isotope[b]	Approximate Expenditures, in Thousands of Dollars
1	^{48}Ca*	446.5
2	^{152}Gd	144.5
3	^{191}Ir*	69.2
4	^{186}Os*	60.0
5	^{193}Ir*	46.2
6	^{187}Os*	42.0
7	^{29}Si	38.3
8	^{40}K	36.4
9	^{204}Pb*	34.5
10	^{102}Pd*	29.2
11	^{196}Hg	28.4
12	^{176}Lu*	27.6
13	^{84}Sr	23.0
14	^{106}Cd	19.5
15	^{64}Ni	18.8
16	^{57}Fe	15.4
17	^{112}Sn*	11.9
18	^{198}Pt*	11.3
19	^{43}Ca	10.7
20	^{200}Hg*	9.2
		1,122.6

[a]Destructive uses only.

[b]Isotopes marked with an asterisk are presently unavailable (see Table 1-3 also).

TABLE 1-3. ISOTOPES UNAVAILABLE FROM OAK RIDGE (as of January, 1982)

$^{24,26}Mg$	$^{108,110,111,113}Cd$
^{30}Si	^{112}Sn
^{33}S	$^{134,135,136}Ba$
^{48}Ca	$^{144,149}Sm$
$^{49,50}Ti$	$^{162,168}Er$
^{60}Ni	^{168}Yb
65Cu	^{176}Lu
^{70}Zn	^{176}Hf
$^{70,74}Ge$	$^{183,186}W$
^{87}Rb	$^{186,187,190,192}Os$
$^{96,98,99,100,101,102,104}Ru$	$^{191,193}Ir$
$^{102,104,105,106,108,110}Pd$	$^{192,194,195,196,198}Pt$
$^{107,109}Ag$	$^{200,201,204}Hg$
	^{204}Pb
	Total: 60

TABLE 1-4. NUMBER OF STABLE ISOTOPES UNAVAILABLE FROM ORNL SALES INVENTORY

	FY77	FY78	FY79	FY80
Depleted	3	19	33	7
Cumulative Total	3	22	55	62

IV. CONCLUSIONS

1. Research in a number of areas of physics and chemistry, in addition to basic studies of the nucleus, depends on the availability of a broad range of separated isotopes. While some research needs are predictable, many others arise on relatively short notice. Scientific progress is now seriously hampered by the unavailability of 60 of the 240 isotopes normally for sale.

It is of utmost importance that the sales inventory of stable isotopes be restored to an adequate level as soon as practicable, so that, for example, $\tilde{>}$ 100 mg needs for material can be satisfied quickly. Due consideration must also be given to the needs of other countries.

Similarly, the Research Materials Collection (RMC) of isotopes available on loan should be replenished and maintained on a continuing basis. Samples should be transferred from the RMC to the sales inventory only when replacements can be provided within one year, as has recently become the policy. Replacements for past transfers should have very high priority.

2. Questions of relative priority will inevitably arise on such issues as the replenishment of depleted stocks and requests for especially large amounts of isotopes. We believe that a scientific advisory committee should be formed to provide advice regarding priorities when mutually exclusive demands arise within the research community in physics, chemistry, and geoscience.

3. For certain uses of enriched isotopes, such as in ion sources, high enrichments is not always required. It may soon be possible to develop isotope separation techniques other than electromagnetic separation to the point where they are able to provide adequate amounts and adequate enrichment of certain isotopes at substantially less expense than is possible with the ORNL Calutrons. When the technical feasibility and cost-effectiveness of such techniques can be demonstrated, they should be implemented to supplement the ORNL program.

2

COMMERCIAL APPLICATIONS

Goal:

Assess the near term (one-to-five-year) needs of domestic and foreign commercial suppliers of radiochemicals and radiopharmaceuticals for electromagnetically separated stable isotopes. Only isotopes purchased to make products for sale and profit are considered in this assessment.

I. ASSESSMENT OF DOMESTIC USERS' NEEDS

A questionnaire was sent to all domestic commercial organizations that had purchased enriched stable isotopes from ORNL during the previous two years. To ensure that proprietary information was not divulged, the questionnaire was to be returned to Dr. E. Newman at ORNL, who compiled totals of the purchases of each isotope. Table 2-1 shows total domestic isotope needs, based on the answers to the questionnaire. Newman estimates that the answers to the questionnaire accounted for approximately 80 percent of the isotopes purchased during 1980 and 1981.

In evaluating domestic needs the Panel on Commercial Applications used the following assumptions:

- During the first plenary session of the Workshop it was pointed out that FDA approval of new radioactive drugs now takes four to five years. It was therefore assumed that the demand for stable isotopes during the next five years would not be affected by the introduction of new radioactive drugs, since there do not appear to be any new radionuclides undergoing scrutiny within FDA. Possibly the Panels on Biomedical Research and Clinical Applications might have indications of new medical uses in prospect.
- It was also assumed that no present use of isotopes would be eliminated because of the introduction of non-radiactive procedures. This may be a riskier assumption than the previous one.
- Domestic use of the four major radionuclides (Tl-201, In-111, Ga-67, and I-123) is not growing as rapidly as improvements in production procedures. As a consequence, it was assumed that there is no need to increase inventory significantly beyond current estimated needs (see Table 2-1). It was anticipated that continued improvements in

TABLE 2-1. PROJECTED DOMESTIC INDUSTRIAL NEEDS FOR STABLE ISOTOPES FROM QUESTIONNAIRES

Element/ Isotope	Minimum Purity Specifications (%)	Inventory (mg)		1982	1983	1984	1985	1986-1990	Uses
		Current	Minimum Needed						
B-10	> 98	0	-	5	5	-	-	-	Spike for isotope dilution
Ca-44	> 97	200	200	500	500	500	500	500	Radiotracer
Cr-50	> 94	200	200	500	500	500	500	500	Radiotracer
Fe-54	> 98	1,000	1,000	1,500	1,500	1,500	1,500	1,500	Radiotracer
Fe-58	> 73	100	100	250	250	250	250	250	Radiotracer
Zn-68	> 95	90,000	355,000	480,000	485,000	480,000	,000	485,000	Radiopharmaceuticals
Se-74	> 95	25	25	75	75	75	75	75	Radiotracer
Sr-84	> 75	200	200	400	400	400	400	400	Spike for isotope dilution
Sn-84	> 99.9	0.5	-	1.4	2.4	2.4	2.4	8-10	Spike for isotope dilution
Rb-87	> 99.9	10	-	2	2	3	3	10	Spike for isotope dilution
Pd-102	> 70	0	1,000	2,000	500	20,000	20,000	50,000	Radiopharmaceuticals
Ru-102	> 98	300	400	100	100	100	100	100	Radiotracer
Ag-107	> 97	1,000	1,000	7,500	7,500	7,500	7,500	7,500	Radiotracer
Cd-112	> 95	25,000	19,500	18,500	21,000	20,000	21,000	23,000	Radiopharmaceuticals
Sn-112	> 80	2,500	1,300	2,000	2,000	2,000	2,000	2,000	Radiopharmaceuticals
Te-123	90+	0	4,000	4,000	4,000	3,000	2,000	4,000	Radiopharmaceuticals; radiochemicals
Sn-124	> 95	200	200	400	400	400	400	400	Radiotracer
Te-124	> 95	33,300	23,000	33,500	35,300	36,000	38,000	42,000	Radiopharmaceuticals
Te-126	> 98	100	100	250	250	250	250	250	Radiotracer
Ba-132	> 20	200	200	1,000	1,000	1,000	1,000	1,000	Radiotracer
Ce-140	> 99	1,000	1,000	2,500	2,500	2,500	2,500	2,500	Radiotracer
Sm-154	> 98	50	50	100	100	100	100	100	Radiotracer
Yb-168	> 13	0	20	250	250	250	250	250	Radiotracer
Tl-203	> 93	500,000	250,000	780,000	780,000	785,000	785,000	785,000	Radiopharmaceuticals
Pb-204	> 99.9	5	-	3	3	5	5	10	Spike for isotope dilution
Pb-206	> 95	0	300,000	300,000	300,000	300,000	300,000	300,000	Radiochemicals; radiopharmaceuticals

production processes will make it possible to meet any increase in the demand for the radionuclides during the next five years with the current rate of stable-isotope production.

- The Panel also assumed that there will be no major new requirements for stable isotopes in other fields during the next five years. The Panel, however, would have preferred to have more information about potential non-medical industrial applications of isotopes.

II. ESTIMATE OF FOREIGN NEEDS

The demand for enriched stable isotopes among foreign radiochemical and radiopharmaceutical manufacturers was estimated by Panel members. These estimates (see Table 2-2) are included because domestic users could be affected if the foreign radiopharmaceutical industry sought to meet all its needs for enriched stable isotopes by purchasing them from ORNL.

Foreign users of stable isotopes purchased from ORNL are located almost entirely in Canada, Japan, and Western Europe. The Comicon (East European) countries appear to be largely self-sufficient in this respect. The estimates of foreign demand are more speculative than those for the United States because of the limited representation of major foreign manufacturers at the Workshop.

The major assumptions used in compiling Table 2-2 were as follows:

- It was assumed that the requirements for stable isotopes at Mallinckrodt's Petten (Holland) facility were included in Mallinckrodt's reply to the questionnaire. If not, the correct figures for Cd-112, Tl-203, Zn-68, and possibly Te-124 in Table 2-2 would be much different.
- Six major isotope-producing cyclotrons (ACL-Canada, Amersham International-United Kingdom, CEA-France, IRE-Belgium, Karlsruhe-West Germany, and Nihon-Medi Physics-Japan) will begin operating in 1982 or early 1983. It was assumed that this will result in a high level of purchasing in order to build up new inventories, but the demand thereafter will fall to a "typical" annual rate.
- It was assumed that the rate at which isotopes are used up is critically dependent on the efficiency achieved in recovering and reusing target material. The Panel had fewer data on this subject than on likely market size. To reduce this uncertainty, DOE should consider seeking estimates from the major foreign commercial users.
- It was assumed that most foreign producers will continue to think of ORNL as their first choice of supply despite the availability of cheaper products from the USSR.

TABLE 2-2. PROJECTED FOREIGN INDUSTRIAL NEEDS FOR STABLE ISOTOPES

Element/ Isotope	Minimum Purity Specifications (%)	Estimated Annual Needs (mg)				
		1982	1983	1984	1985	1986
Calcium-40	99.9	2,000	2,000	2,000	2,000	2,000
Calcium-44	99	500	500	500	500	500
Calcium-46	40	35	35	35	35	35
Chromium-50	96	1,500	1,500	1,500	1,500	1,500
Iron-54	97	1,000	1,000	1,000	1,000	1,000
Iron-58	80	1,000	1,000	1,000	1,000	1,000
Nickel-58	99	30,000	30,000	30,000	30,000	30,000
Nickel-62	97	3,500	3,500	3,500	3,500	3,500
Zinc-68	99	100,000	60,000	65,000	65,000	70,000
Selenium-74	98	500	300	200	200	200
Strontium-84	75	150	150	150	150	150
Strontium-88	99	15,000	15,000	15,000	15,000	15,000
Cadmium-112	98	50,000	35,000	35,000	35,000	35,000
Cadmium-114	99	500	500	500	500	500
Tin-112	80	1,000	1,000	1,000	1,000	1,000
Tin-118	97	1,000	1,000	1,000	1,000	1,000
Tin-124	96	150	150	150	150	150
Antimony-121	95	10	10	10	10	10
Tellurium-124	95	10	10	10	15	20
Barium-130	35	50	50	50	50	50
Neodymium-146	-	20	20	20	20	20
Europium-151	97	150	150	150	150	150
Gadolinium-152	20	10	10	10	10	10
Ytterbium-168	20	200	200	200	200	200
Hafnium-180	92	20	20	20	20	20
Tungsten-184	98	20	20	20	20	20
Thallium-203	95	100,000	50,000	50,000	50,000	50,000

- Although new products for medical use can be introduced more quickly in other industries than in the U.S., it was assumed, given the absence of evidence to the contrary, that there are no new radioactive pharmaceuticals under development in foreign countries that would lead to major changes in the demand for stable isotopes during the next five years.

III. IMPACT ANALYSIS

Radiopharmaceuticals produced from enriched stable isotopes supplied by the Calutron facility at ORNL are used in about 600,000 medical procedures each year in the United States. A temporary or permanent disruption of the supply of stable isotopes to the domestic radiopharmaceutical industry could curtail, if not eliminate, the use of such diagnostic procedures as the thallium heart scan, the gallium cancer scan, the gallium abscess scan, and the low-radiation-dose thyroid scan. The word "could" in the preceding sentence is underlined because an alternative source of enriched stable isotopes does exist in the USSR. If the domestic supply of isotopes was cut off, the U.S. radiopharmaceutical industry could probably meet its needs by purchasing isotopes from the Soviet Union, but this would presumably be true only if such trade benefited the USSR. Such purchases could be halted in the event of political disagreements between the United States and the Soviet Union.

Alternative starting materials could, in theory, eventually be developed for both the thallium and gallium scans. The development of a new technology for these purposes, however, would take at least five years and would be expensive. Hence, any disruption of the supply of enriched isotopes from ORNL and the resulting unavailability of critical nuclear medicine procedures would have a dramatic negative effect on the level of health care in the United States.

IV. COMMERCIAL USERS' PERCEIVED PROBLEM AREAS

It is not the intention of the Panel on Commercial Applications to recommend operating policies to DOE. The Panel does believe, however, the following points should be considered by DOE in its evaluation of the needs of industrial suppliers of radionuclides and radiopharmaceuticals. The Panel also believes that the points discussed below should be considered by DOE in its long-range plans regarding the Calutrons at ORNL.

- Potential impact on medical practice. It is apparent from the papers delivered at the plenary session that commercial requirements account for nearly 80 percent of the operating time of the Calutron facility. These operations should not be considered to be merely for the purpose of preparing stable isotopes for commercial concerns but as a cornerstone in the preparation of diagnostic agents that will benefit the health of the public.
- Assurance of supply. The Panel members are concerned about the possibility of an interruption in the supply of isotopes

from ORNL because of defense or other programmatic needs of the federal government. Such interruptions have happened before and presumably could happen again.

- o Production capacity. The capacity of the Calutrons at ORNL to produce isotopes appears to be more than adequate. The problem in meeting demand is a lack of trained manpower. Consideration should be given to commercial participation and financial support for trained manpower to assure that the supply of stable isotopes will not be affected by governmental programmatic needs.
- o Predictability in pricing policy. Commercial users of isotopically enriched materials have difficulty with DOE's current policy of determining the price of the materials after they have been produced and shipped to the buyer. This procedure does not conform with normal business practices and is an impediment to commercial planning. Particularly troublesome have been the wide price fluctuations that have occured; they make rational planning for isotope acquisition and utilization very difficult.
- o Analysis of needs. The Panel believes that an "analysis of needs" should be a continuing process, perhaps taking the form of an annual review involving both DOE and commercial users of isotopes. This might be accomplished by means of a questionnaire and Workshop as was done in the preparation of this study.
- o Sales priority. Commercial users are somewhat apprehensive about the possibility of a sudden depletion of the inventory of a particular isotope as a result of one large sale to a single customer. DOE might consider developing a procedure for fair allocation of any isotope that would be out of stock for an extended period of time if the entire supply were purchased by a single buyer..
- o Inventory information. Information regarding the availability of any particular enriched isotope can only be obtained in general terms by a phone call to ORNL. To establish orderly program and cost projections, commercial users would like to receive information periodically regarding the current and anticipated supply of the most widely used isotopes.
- o Possible impact of non-medical commercial users. Although every attempt was made to include all purchasers of electromagnetically separated isotopes in the survey, no responses were received from non-medical commercial users. Although, based on past ORNL sales records, their needs are estimated to be less than 10 percent of the total sales, the Panel was concerned about its inability to comment explicitly on the impact that advances in the non-medical area might have on the overall forecast.
- o Potential exchange program. Consideration should be given to the development of orderly procedures for transferring isotopes among ORNL's Research Materials Collections, its Sales Inventory, and surplus commercial pools, as a way of maximizing isotope availabilty without jeopardizing the

interests of any user. This might help to eliminate the concern expressed by the research community about the depletion of supplies at ORNL because of commercial purchases.

- Alternate production methods. The Panel would like to see improved communications between the DOE offices concerned and those groups who are developing, or who have developed, alternative separation procedures with the potential of relieving some of the high-volume demand for certain Calutron-produced isotopes.

3

BIOMEDICAL RESEARCH APPLICATIONS

I. INTRODUCTION

The biomedical research Panel believes that the Calutron facility at Oak Ridge is a national and international resource of immense scientific value and of fundamental importance to continued biomedical research. This resource is essential to the development of new isotope uses in biology and medicine. It should therefore be nurtured by adequate support and operated in a way that optimizes its services to the scientific and technological community.

The Panel sees a continuing need for a reliable supply of a wide variety of enriched stable isotopes. The past and present utilization of stable isotopes in biomedical research is documented in Appendix 7. Future requirements for stable isotopes are impossible to document, however, because of the unpredictability of research itself. Nonetheless we expect the demand for isotopes to increase in parallel with the continuing expansion of biomedical research as a whole. There are a number of promising research projects at the present time, and these are expected to lead to an increase in production requirements. The Panel also believes that a high degree of priority should be given to replacing the supplies of the 65 isotopes (out of the 224 previously available enriched isotopes) no longer available from ORNL.

II. CURRENT AND NEAR-TERM FUTURE NEEDS FOR STABLE ISOTOPES AND DERIVED RADIOISOTOPES

A. Stable Isotopes

Enriched stable isotopes are a key tool in many areas of biomedical research. Indeed, some investigations can only be carried out with stable isotopes because of the unsuitable characteristics of the radionuclides of the element in question. Investigations utilizing enriched stable isotopes range from studies of the minerals essential for human health, as well as those of toxicological significance, to spectroscopic studies with isotopes of non-zero nuclear spin. During the past four years there has been considerable growth in the use of stable isotopes in these and other areas. Thanks to increased awareness of the role played by minerals in human health and as etiological factors in diseases (such as osteoporosis, and possibly atherosclerosis and cancer), there has been a figurative explosion of research into the absorption, metabolism, and other functions of minerals in human biochemistry under various pathological conditions. Prior to 1978 there were no reports of the use of ^{68}Zn and ^{70}Zn in human

metabolic studies, but during the past two years one laboratory alone has utilized 1.5-2.0 g of each isotope in such studies. Other techniques, including nuclear resonance spectroscopy employing ^{113}Cd, ^{111}Cd, ^{77}Se, ^{43}Ca, and ^{25}Mg, have demonstrated a clear applicability to important studies of human metabolism, growth regulation, membrane structure, and nucleic acid synthesis. Such studies, together with similar applications of electron paramagnetic spectroscopy and Mössbauer spectroscopy, indicate that quantities on the order of one gram of some 18 enriched stable isotopes will be needed in the immediate future. The problem of stable isotope availability for use in biomedical research has already become acute. There are severe shortages of ^{25}Mg, ^{26}Mg, ^{43}Ca, ^{46}Ca, ^{50}Ti, ^{67}Zn, ^{70}Zn, ^{74}Se, ^{77}Se, ^{78}Se, ^{102}Pd, ^{111}Cd, ^{113}Cd, ^{190}Os, ^{141}Sm, and ^{185}Re. Research has been delayed, or even abandoned, as a consequence of this problem.

B. Derived Radioisotopes

Radioisotopes are utilized in biomedical research principally for the preparation of radiopharmaceuticals for in vivo studies of physiological function. These radioisotopes are produced from stable isotopes by a variety of induced nuclear reactions. Generally, the highest possible isotopic enrichment of the target is either preferred (to maximize yield) or required (to eliminate or minimize radionuclidic impurities). More specifically, ultrahigh isotopic enrichments of ^{123}Te ($\sim$87 percent) and ^{124}Te ($\sim$99 percent) are required to produce ^{123}I containing the lowest possible level of ^{124}I. High-purity ^{123}I reduces the radiation burden on patients, improves the quality of the diagnostic procedure, and extends the shelf-life of the radiopharmaceutical. The medical community must now accept rather poor enrichment (90-96 percent) of ^{124}Te and a very limited supply of highly enriched ^{123}Te.

There is an immediate need for 95 percent isotopic enrichment of ^{190}Os for continued research and development of the ^{191}Os - ^{191m}Ir generator. A ^{191}Os - ^{191m}Ir generator typically requires 10-25 mg of enriched ^{190}Os. An annual requirement of 100-200 g of enriched ^{190}Os is projected once the generator is adopted for clinical radionuclide angiocardiography.

Lambrecht (Appendix 7) documents the demand in radiopharmaceutical research for 47 enriched stable isotopes in quantities ranging from 50 to 50,000 mg per year. For example, quantities up to 10 g or greater are now required for enriched ^{76}Se, ^{77}Se, and ^{78}Se; ^{79}Br and ^{81}Br; ^{121}Sb and ^{123}Sb; ^{121}Te, ^{123}Te, and ^{124}Te. Efforts to develop potential radiopharmaceuticals with derived radioisotopes have concentrated on labeling analogs of fatty acids, steroids, drugs active on the central nervous system, monoclonal antibodies, and various inorganic chemical species with (primarily) ^{123}I, ^{75}Br, ^{77}Br, ^{73}Se, ^{75}Se, ^{97}Ru, and ^{77}Kr.

Research into trace mineral metabolism, biochemistry, and nutrition science now requires isotopes of 28 elements. Research in micronutrients or toxins will mean a need for at least five more, and heavy metal radioisotopes will also be needed in the future. Presently, there is a need for 0.5 to 10 g of ^{25}Mg, ^{26}Mg, ^{46}Ca, ^{67}Zn, ^{70}Zn, ^{74}Se, ^{76}Se, ^{77}Se, and ^{78}Se.

Appendix 7 presents quantitative estimates (in grams per year 1982-1985) for the established needs of particular enriched stable isotopes.

III. CONCLUSIONS

A. Stable Isotope Users Advisory Committee

The biomedical research Panel recognizes that the allocation of enriched stable isotopes to purchasers and the scheduling of separations at ORNL are complex tasks. It is essential, however, that a consistent and equitable policy toward all users be developed and implemented. We suggest the creation of a scientific advisory committee composed of representatives of the major user groups to advise DOE on the formulation of this policy. In addition, this committee could review past and present production operations and provide advice about future enrichment schedules. This would ensure that the critical needs of users are met and that a complete inventory of separated isotopes is maintained. This committee, however, should not be assigned the task of establishing priorities for the replenishing of the Research Materials Collection nor for the distribution of materals from that pool. Those matters could best be addressed by a separate group.

B. Level of Support for the Calutron Facility At Oak Ridge

This Panel is aware that current separation operations do not utilize the entire capacity of the Calutron facility. If additional funding were available, throughput could be expanded by at least a factor of two. We strongly urge that funding be provided to permit this expansion within the shortest possible time to relieve critical current isotope shortages.

Appendix 7 documents a major shift from reactor production in which enriched stable isotopes are used for a number of important products, such as the ^{191}Os - ^{191m}Ir biomedical generator) to cyclotron production of new radioisotopes, which depends much more heavily on stable isotopic feed stock. This shift, particularly in the industrial sector, has played a major role in the increase in demand and has led to the critical shortages of research materials.

The increased use of enriched stable isotopes by foreign countries has also had a definite impact on the available supply of isotopes from ORNL. Japan is reported now to depend almost entirely

on the United States for its supply of stable isotopes, since only small amounts are available, via French intermediaries, from the Soviet Union. Canada is reported to be experiencing a major shift from reactor-to accelerator-produced nuclides similar to that in the United States.

The need for enriched stable isotopes outside the United States, especially within the research community, must be considered, as the United States in most cases is the sole source of supply, and the importance of such research for all of us can be readily documented.

C. Priorities in Calutron Operation

DOE's present policy on the sale of stable isotopes at ORNL is "first come, first served." We consider it important to replace this policy with a policy designed to deploy Calutron resources to serve the needs of all stable isotope users in optimum fashion. We proposed above the formation of an advisory committee to assist in setting priorities.

We are profoundly concerned over the erosion of the inventory of separated stable isotopes at Oak Ridge. Not only does this sales and research material inventory represent a unique scientific and technological resource, but it also represents a "cushion" to maintain the availability of stable isotopes (of unpredictable identity) for the changing needs of research in the face of the finite response time of the Calutron program to altered demands. We urge that a proportion of the operating time and budget of the Calutron facility be reserved to rebuild stocks of the depleted isotopes in the shortest possible time.

We also believe that sales to one category of users should not have a disproportionately severe impact on ORNL's ability to meet the needs of another. This goal could be accomplished by careful surveillance of demand--more specifically, the needs of the research community--and timely feedback of this information to the Calutron facility's staff. Alternatively, a policy of reserving some minimum fraction of total production capacity for each category of users might be implemented.

It is also a matter of some concern to this Panel that the foreseeable expansion of demand arising from an increase in medical radioisotope utilization may eventually exceed the capability of the ORNL production facility, even running at full capacity. The production of a wide spectrum of separated isotopes--which electromagnetic separation is uniquely able to accomplish--is necessary to ensure the widest possible range of research activities. This production should not be unreasonably restricted by the need to produce isotopes for high-volume (i.e., industrial) users.

We therefore believe that funds should be devoted to research on other enrichment techniques potentially suitable for the large scale separation of specific nuclear species.

Examples of such promising approaches are:

- o Gaseous centrifuge techniques for osmium nuclides, which are difficult to separate by means of electromagnetic methods.
- o Liquid-phase thermal diffusion now being used for sulfur, chlorine, and bromine nuclides, and potentially useful for some other elements.
- o Chemical exchange separation, which is potentially applicable to calcium and might be developed to the point where it could satisfy the large potential demand for ^{48}Ca as well as magnesium and zinc nuclides.
- o Plasma centrifuge techniques, which show promise for copper separations.
- o Laser separation, which holds promise for separating isotopes of certain metallic elements, and so may possibly be used specifically to produce separated ^{203}Tl, production of which now constitutes a major demand on Calutron operation.

We emphasize here that any funds allocated for the development of new separation methods should not come at the expense of present funding for the Calutron facilities. That valuable resource should be preserved and expanded so as to maximize the scientific and technological return on the investment which it represents.

D. Self-Sufficiency

The original purpose of the isotope enrichment program at Oak Ridge was to serve the needs of the research community through the establishment and maintenance of the Research Materials Collection. This activity continues to be supported by federal nuclear research funds, and this Panel fully endorses continuance of this effort. What concerns us is the effect that the rising needs of clinical medicine and industry, both in the United States and in other countries, is having on the Calutron program. The extent to which these additional activities are self-supporting should be closely examined.

4

CLINICAL APPLICATIONS

I. INTRODUCTION

The Oak Ridge Calutron facility has been a critical factor in the development and subsequent production of a majority of currently useful medical radionuclides. Its importance along with other steps of production (e.g., bombardment in cyclotrons or reactors) is, however, largely unrecognized by the physicians who administer these agents. Unfortunately, the facility's very success seems to threaten its continued existence as a balanced producer of isotopes for both research and commercial users. The medical community believes that replenishing and maintaining a full inventory of stable isotopes for research purposes is critical. No less critical is the need for continuing production of large quantities of isotopes for medical purposes.

II. PAST AND CURRENT USES

The story of the development of technetium-99m illustrates how basic research at a National Laboratory can result in major advances in biomedical research and the practice of medicine. It illustrates the key role played by a stable isotope, Mo-98, in the commercial development of an important group of radiopharmaceuticals, a role that was impossible to foresee.

In the 1950's, scientists in England were producing the radionuclide ^{132}I for use in thyroid research by distilling it from the parent nuclide, tellurium-132. W.D. Tucker and his associates at Brookhaven National Laboratory then invented the radionuclide generator in 1958 to facilitate the separation process. Tellurium-132, a fission product, was found to contain a trace contaminant, which proved to be technetium-99m. Although no one at that time realized the possible uses of the two nuclides, the Mo-99/Tc-99m generator was advertised in the Brookhaven National Laboratory Catalogue of 1960, in letters two inches high. Except for a study by Shellabarger of the thyroidal uptake of the pertechnetate ion, nothing of major significance happened until 1963, when Harper and Richards recognized that the photon energy (140 kev) and half life (six hours) of technetium-99m were nearly ideal for nuclear imaging. Over the next several years, radiopharmaceuticals incorporating technetium-99m were developed for the study of the brain, liver, thyroid, lungs, skeletal system, kidneys, heart, and biliary system.

The Brookhaven group had originally produced ^{99}Mo from fission, but the resulting product was contaminated by ruthenium-106 and iodine-131. To eliminate this problem, molybdenum-99 was then produced by neutron activation of molybdenum-98, which was available

in four-fold enrichment from ORNL. This allowed commercial producers to use larger and more efficient generators. The sales of molybdenum-98 rose to a peak value of $48,000 per year in 1977. Subsequently, the demand for enriched Mo-98 fell to negligible levels as clinical needs for higher specific concentrations of technetium-99m led to the revival of production by the fission method. Today sales of technetium-99m radiopharmaceuticals amount to about $50 million per year in the United States, where approximately five million patient studies with these radiopharmaceuticals were performed in 1981. Nonetheless, this story shows how the Calutron facility at ORNL provided an important alternative approach for producing molybdenum-99 at a critical time in the development of the radiopharmaceuticals most commonly employed in medical practice.

The introduction of thallium-201 into clinical practice was also made possible by the production of stable isotopes at Oak Ridge. The radionuclides that first had been used to study the blood supply of the heart were isotopes of potassium, rubidium, and cesium, all produced by ORNL. These radionuclides had characteristics that made them less than totally satisfactory, although potassium-43 was used for a while in the detection of coronary heart disease. As the search for a better tracer continued, Harper recognized that thallium was an analogue of potassium. By producing a mixture of thallium radioisotopes by proton bombardment of mercury, he was able to demonstrate marked localization of the tracer in heart muscle. Lebowitz at Brookhaven then developed a method for producing pure thallium-201 from the stable isotope thallium-203. Subsequently, four-fold enriched Tl-203 was used as a precursor. Sales of Tl-203 increased from $44,000 a year in 1975 to $2,114,900 in 1981. It is estimated that sales of thallium-201 in the United States now amount to over $30 million annually. More than 250,000 patients received thallium-201 in 1981.

The third nuclide to be discussed here is gallium-67. This agent was used initially to study the skeletal system by Hayes and coworkers at ORNL. It was then observed to accumulate in certain malignancies, and today is widely used in the diagnosis of both tumors and infections. Sales of the five-fold enriched Calcutron produced precursor nuclide Zn-68 amounted to more than a quarter of a million dollars in 1981.

Examples like these demonstrate that many advances in nuclear medicine and radiopharmaceutical production would not have occurred without the stable isotope program at ORNL.

III. UNMET AND FUTURE NEEDS

Enriched 190Os is required for further development of an osmium-iridium generator for study of the heart. The short-lived (5 sec) iridium-191m radionuclide shows exceptional promise for use in the diagnosis of congenital heart disease in infants (with increased sensitivity and specificity of diagnosis and considerable reduction in

radiation dose) and for studying isolated ventricular function in adults. Enriched 190Os will be required to ensure efficient production, generator operation, and continuous infusion of ^{191m}Ir. The depletion of the stock of 190Os impedes further development of this promising generator; uncertainties of future production will limit our ability to introduce the technique into clinical practice.

Iodine-123 of high purity and specific activity is needed in large quantity for the further development of tracers that have promising clinical applications. These include the labeling of monoclonal antibodies and antibody fragments for tumor detection, the labeling of site-specific receptor binders, and the iodination of neuropharmaceuticals for measurements of regional cerebral blood flow and function, especially using single photon emission tomographic methods. The use of positron-emitting radioiohalogens, such as bromine-75/77, is also under study.

Radionuclides of specified characteristics will be needed to realize further advances in their use for therapeutic purposes. Among those currently identified is iodine-131 of high specific activity. Others, such as dysprosium-165 (now undergoing trials for radioactive synovectomy), indicate the potential utility of relatively high Z materials.

Although the demand for stable isotopes for use in nuclear magnetic resonace (NMR) spectrometry, either for measurements of biochemical events in vivo or for NMR imaging, is currently unknown, these uses could possibly require the production of considerable quantities of enriched material.

Because current needs for enriched isotopes are rapidly changing and future needs are unpredictable, a full inventory at ORNL is a necessity for the medical and research communities. This will require greater use of the Calutrons' production capacity and continue operation of the facility by the federal government, since it seems unlikely that the private sector would provide the full range of isotopes required for continued progress. It is imperative that ORNL's inventory be restored and upgraded, in keeping with the facility's importance as a national resource. The stability of the program requires that both routine clinical and medical research needs be met. An inability to respond quickly to new developments will seriously reduce the realization of opportunities in this field.

IV. CONCLUSIONS

The continued availability of the isotopic materials necessary for optimal health care, now and in the future, can only be achieved by taking the following actions:

1. Stocks of all the stable isotopes from which products for research and patient care are derived must be expanded and maintained. Adequate inventories of each of these isotopes should encourage research and assure dependable sources for medical uses. This will require the utilization of unused Calutron capacity.

2. All facilities, including the Calutrons, capable of furnishing products to meet these needs should be identified and described. A national strategy for stable isotope production should be developed that takes alternative separation methods into account. This would help to ensure that limitations in Calutron production capabilities do not hamper progress or research options. Alternative separation methods offer the potential for producing a limited, but significant, number of stable isotopes when large quantities and relatively low enrichments are required. Federal support for the research and development of these alternative methods should be continued.
3. An advisory committee should be created to set realistic goals, to evaluate resources, and coordinate overall efforts. This committee should represent all those with an interest in the production of isotopes, including the research community, physicians, industry, and government agencies. Such a committee is needed to achieve balance between production for research and routine needs and to provide flexibility in meeting rapidly changing requirements.

APPENDIXES

Department of Energy
Washington, D.C. 20545

APPENDIX 1

January 16, 1981

Dr. Herbert Friedman, Chairman
Assembly of Mathematical and Physical Sciences
National Research Council
2101 Constitution Avenue, NW
Washington, D. C. 20418

Dear Dr. Friedman:

Changing priorities in the production of and demand for stable isotopes and radioisotopes derived from them have led to problems in the Federally-funded stable isotope production program. Earlier, this program served the basic nuclear research community, but over the past several years the demand for isotopically enriched materials for applications in the medical and industrial communities has greatly increased. There is a need for exchange of information amongst the various sectors of users and the Federal production program. We feel that a Workshop on Applications of Stable Isotopes and Derived Radioisotopes, attended by 30 or 40 appropriate representatives of the user groups and the production program, would provide the needed interaction and would result in the information needed for sounder support of the program.

Would the Subcommittee on Nuclear and Radiochemistry of the Assembly's Committee on Chemical Sciences be willing to consider holding such a workshop in the Fall of 1981, with some financial support from the Department of Energy and, possibly, the National Institutes of Health? If you are inclined to carry out such a project, I should be pleased to receive a suitable proposal.

Sincerely,

Elliot S. Pierce, Director
Division of Chemical Sciences
Office of Basic Energy Sciences

cc: Prof. G. R. Choppin
Dr. A. Schriesheim
Prof. J. L. Kinsey
Dr. William Spindel

APPENDIX 2

PANEL PARTICIPANTS

Workshop on Stable Isotopes and Derived Radioisotopes
February 3-4, 1982

National Academy of Sciences
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Panel 1:	Research Applications in Physics, Chemistry, and Geoscience
Plenary Speaker:	Michael S. Zisman, Lawrence Berkeley National Laboratory
Chairman:	John P. Schiffer, Argonne National Laboratory
Rapporteur:	David K. Scott, Michigan State University
Participants:	I. Lynus Barnes, National Bureau of Standards Joseph Cerny, III, Lawrence Berkeley National Laboratory Gregory R. Choppin, Florida State University Robert Chrien, Brookhaven National Laboratory Kate Glover, A. E. R. E. Harwell Rolfe H. Herber, Rutgers University Günther Herrmann, Johannes Gutenbert Universität Darleane C. Hoffman, Los Alamos National Laboratory A. Paulsen, Central Bureau of Nuclear Measurements Raymond G. Wymer, Oak Ridge National Laboratory William B. Yelon, University of Missouri Research Reactor
Panel 2:	Commercial Applications
Plenary Speaker	J. Calvin Brantley, New England Nuclear Corporation
Chairman:	Henry H. Kramer, Medi-Physics, Inc.
Rapporteur	Ronald D. Finn, Mt. Sinai Medical Center
Participants	Homer Hupf, RadPharm G. Sargent Janes, Avco-Everett Research Laboratory, Inc. John Ogle, Amersham Corporation Greg Rocco, New England Nuclear Corporation John Russell, Georgia Institute of Technology Eric Stohler, Stohler Isotope Chemicals, Inc. D. R. Van Deripe, Mallinckrodt, Inc. William Wilkes, Monsanto Research Corporation

Panel 3: Biomedical Research Applications

Plenary Speaker: Richard M. Lambrecht, Brookhaven National Laboratory
Chairman: Alfred P. Wolf, Brookhaven National Laboratory
Rapporteur: Harold A. O'Brien, Jr., Los Alamos National Laboratory

Participants:
David A. Goodwin, Palo Alto VA Hospital
Yukio Murakami, Kitasato University
Brian D. Pate, University of British Columbia
Roger S. Powell, National Institutes of Health
William M. Rutherford, Monsanto Research Corporation
Vernon R. Young, Massachusetts Institute of Technology

Panel 4: Clinical Applications

Plenary Speaker: Richard C. Reba, George Washington University Medical Center
Chairman: S. James Adelstein, Harvard University Medical School
Rapporteur

Participants
Harold Adkins, State University of New York, Stony Brook
William H. Beierwaltes, University of Michigan Hospital
Frederick J. Bonte, University of Texas, Dallas
Paul V. Harper, University of Chicago
Paul B. Hoffer, Yale University School of Medicine
John Kuranz, G. D. Searle and Company
Peter Paras, Food and Drug Administration
William Roos, Monsanto Research Corporation
James J. Smith, Veterans Administration
Henry N. Wellman, University of Indiana Medical Center

APPENDIX 3

THE U.S. STABLE ISOTOPE PROGRAM

Gregory R. Choppin
Florida State University

In 1943 the Manhattan Engineering District awarded a contract to Tennessee Eastman Corporation to operate a secret electromagnetic facility, Y-12, near Oak Ridge, Tennessee. The purpose of the Y-12 plant was to use mass spectrometry to obtain large quantities of isotopically pure uranium-235. By 1945 the Y-12 facility employed nearly 25,000 people and had more than 1,100 separating units. However, by then the gaseous diffusion process had been shown to be a less expensive method of obtaining ^{235}U. When the war ended, therefore, Y-12 was declared obsolete, and a shutdown of the plant began.

The possibility of using part of the plant to produce small quantities of enriched isotope materials for basic and applied research was then discussed by representatives of Manhattan Engineering District and Tennessee Eastman Corporation. E. P. Wigner wrote in support of the program:

> In our opinion, the work now being done ... at the Y-12 plant is and promises to continue to be, scientifically, one of the most important projects now under way in this country. We should have, as the very basis of future work in nuclear physics and chemistry, knowledge of the various cross sections of pure stable isotopes. Eventually, separated isotopes of the elements may provide invaluable raw material for the production by pile, or other irradiation, of radioisotopes of value in science, medicine and industry. Since we believe that the stable isotope program at Y-12 is, today, scientifically more important and soon will be more important on every count than the uranium isotope separation, we wish that greater emphasis could be placed on it.

Further discussions in late 1945 and early 1946, and strenuous efforts by P. W. McDaniel, led to the initiation of a stable isotope program with a pilot plant of four Calutrons (Calutron = California University Cyclotron). Two were of 48-inch radius (α Calutrons), and two were of 24-inch radius (β Calutrons). An additional 72 β Calutrons were retained in a "production" building.

The Calutrons of Oak Ridge operate according to the principles of electromagnetic acceleration in circular orbits formulated by E. O. Lawrence in the development of cyclotrons. Impurities in isotopes separated by one mass unit have, on occasion, been confined to less than 1 part per million and even to the parts-per-billion range. The enrichment factors for various isotopes range from about 30 to as high as 80,000 in a single pass.

The separator tanks for the alpha Calutrons measure 12 feet by 8 feet by 28 inches and weigh 10 tons. The beta tanks are 6.5 feet by 5 feet by 23 inches and weigh about 9 tons. The magnetic field strength for uranium separation is 3,200 gauss in the alpha separators and 6400 gauss in the betas. The weights of the conducting windings range between 10 and 17 tons for both the alpha and beta coils.

By using the four regular Calutrons and extending the temperature range of the ion sources from the uranium downward to room temperature and upward to 2800°C, the operators of the plant were able by the mid-1950's to process all elements with naturally occurring stable isotopes except osmium, which was first processed in 1960.

By 1959 the need for enriched stable isotopes had increased so much that the quantities required could no longer be produced by the four Calutrons, and the Atomic Energy Commission (AEC) put the 72 beta Calutrons in the production building into use. These separators are positioned in two rectangular tracks, each track containing 36 Calutrons in two 100-foot-long parallel arrays. The two sides of each track are joined together by 30-foot-long, 160-ton iron yokes to make an overall closed magnetic circuit except for the gaps that hold the Calutrons.

The production of isotopes of heavy elements at Oak Ridge, and the separation of isotopes of light elements at Mound Laboratories and at Los Alamos, have provided a broad spectrum of stable isotopes for use in the physical and biological sciences as well as for medical and technological purposes.

In 1968 the Committee on Nuclear Sciences of the National Research Council under the chairmanship of D. A. Bromley appointed an ad hoc panel to study "the national uses and needs for separated stable isotopes." G. C. Phillips headed the panel, whose recommendations were as follows:

"Primary Support"

> The AEC Research Division should continue to provide primary support for the entire program so that production will not be directly and immediately controlled by current sales. While responsibility for the program rests with the AEC Research Division, an effort should be made to

make the program a more self-sustaining one.

To endanger the program by making its continued operation contingent upon receipts would, at this time, seem extremely unwise. There is general agreement, however, that the future development of the program should take into account the desirability of reducing the unreimbursed support obtained from the AEC Research Division. Apart from the scientific justification for the continued direct support by the AEC, this committee believes that the entire program must be viewed as a national resource of incalculable value to the United States. While it requires less than a million dollars to rehabilitate the Calutrons now in use in the separated isotope program, the actual cost of these separators was of the order of 50 million dollars, and their replacement now (i.e., 1968), no doubt, would be more than 100 million. The opportunity to apply such machines for scientific purposes so cheaply will never occur again.

"Inventory"

The present inventory should be re-evaluated to reflect replacement cost at current operating efficiency, not the accumulated cost of the program. Low enrichment items should be appropriately reduced in value in proportion to reduced demand. Where the inventory of a low enrichment nuclide has been replaced by a high enrichment nuclide, the low enrichment should be depreciated to its asset value as an enriched feed material for additional Calutron passage.

"Loan Program"

Since at least one-half of the Calutron time is spent on the production of nuclides designated for the loan pool, it might seem appropriate that a share of the cost of the operation of the facility be borne by the loanees and the committee has considered this possibility. However, the panel does not recommend that a charge be made for loans from the pool. Nevertheless, some revision of the loan program must be carried out to prevent the holding of nuclides for unconscionable long periods. Under no circumstances should any nuclide be loaned to an individual for a continuous period of more than 24 months without specific scientific review.

Relative prices should be based on production costs with charges allocated among isotopes according to demand. Ideally, one would multiply all prices by an appropriate factor so that last year's sales plus rentals

would recover the next year's budget. Based on last year's sales (i.e., 1967), such a policy would result in a two-fold increase in the price of isotopes. After carefully considering such a major price increase to isotopes consumers, the committee has rejected such a proposal. While such a policy would relieve the AEC Research Division from subsidizing the program, the net effect would be to increase Federal expenditures in other agencies.

"Program Emphasis"

Scientific and technical arguments have been given that indicate that new and significant emphasis should be placed on the following areas of the program:

1. Increasing capabilities of producing high purity materials by improved techniques and by multiple-pass separations.

2. Expand AEC efforts in the production of separated light elements (especially those with biological and medical importance) if methods of larger scale, less expensive production, can be developed.

3. Study ways to expand the present program capabilities of production to be able to handle foreseeable rapidly growing needs --expecially in medical applications.

Most recently, the Committee on Chemical Sciences of the NRC reviewed the stable isotope program with emphasis on its relationship and importance to the research programs of the Department of Energy's Office of Basic Energy Sciences. The Committee noted that three circumstances have diminished governmental support for isotope use: (a) the decision, made when the AEC still existed, to encourage private-sector organizations to produce isotopes; (b) the erosion of overall financial resources for AEC (later ERDA) programs, with consequent effects on activities deemed less than vital to the agency's mission; and (c) the successive transfer of isotope operations to ERDA and then to DOE, agencies without the commitment to isotope research that characterized the AEC.

The Committee reported that:

...these influences have not yet seriously affected the availability of isotopes for research; but there are some areas of concern. (a) The stockpile of stable isotopes is being depleted. This collection of the building blocks of all substances is an invaluable asset for both practical

and theoretical research, and scientific common sense calls for enlarging it rather than permitting it to disappear. (b) The production of certain radioisotopes is inadequate, and the production capability is seriously affected by any outage of the small numbers of reactors and accelerators devoted to that purpose. (c) The fiscal policies applied to isotope production led to a declining effective effort, and that is consonant neither with the importance of isotopes to research nor with the massive scientific and technological efforts needed to cope with the problems of energy.

The principal recommendation of the Committee was that the DOE should reaffirm its responsibility for an adequate supply of separated isotopes for research, with DOE's Office of Basic Energy Sciences (BES) being given adequate funding to oversee the production of these materials, to arrange for the necessary development of new or improved processes to meet changing demands, and to support research appropriate to these activities.

Dr. Anthony Turkevich was a member of the Committee on Chemical Sciences, NRC, and the liaison with our Subcommittee of Nuclear and Radiochemistry. He initiated discussions in the Subcommittee which, after further exploration of the problems with scientists and administrators of BES, particularly Dr. Elliot Pierce, and of ORNL, led to the proposal for this workshop. We hope that our discussions at this meeting will ensure diverse and adequate supply of stable isotopes for use by the scientific, medical and industrial communities.

In conclusion, on behalf of the subcommittee, I wish to thank Drs. G. Friedlander and H. Wagner for organizing the workshop and Dr. W. Spindel for seeing that it is happening.

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APPENDIX 4

THE STABLE ISOTOPE ENRICHMENT PROGRAM AT OAK RIDGE NATIONAL LABORATORY*

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ABSTRACT

By means of the isotope separation program at Oak Ridge National Laboratory (ORNL), electromagnetically enriched stable isotopes are made available to the worldwide scientific community. Among the topics discussed in this paper are the methods of enriching isotopes and the limitations that apply to the quantity and final assay of the separation products. A brief description of each production step, from the selection and preparation of initial feedstock to the recovery and distribution of isotopically enriched material, is presented. The future of the facility, the continued supply of enriched isotopes, and the response of the program to new and changing requirements are emphasized.

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I. INTRODUCTION

The existence of the electromagnetic isotope separation facility at Oak Ridge National Laboratory (ORNL) and the availability of enriched stable isotopes from ORNL's Isotope Sales Office are familiar to most research and commercial laboratories throughout the world. The purpose of this paper is to review the goals of the program, the technology employed to produce separated isotopes, and the restrictions and limitations that apply to both isotope quantity and isotopic purity. The discussion will be limited to the approximately 60 multi-isotopic elements made available by the operation of the facility. The isotopic enrichment of light elements, notably hydrogen, lithium, and boron, as well as the production of isotopes of the gaseous elements available from the Isotope Sales Office at Mound Laboratory, will not be discussed.

The objective of the ORNL isotope program is to *enrich stable isotopes, selected radioactive isotopes, and heavy-element isotopes for use in research and development and in commercial activities.* To accomplish this objective, ORNL, at the direction of the Department of Energy (DOE), operates the electromagnetic isotope enrichment facility. This facility consists of very high current mass separators, known as Calutrons, which were used to provide enriched uranium in the 1940's. Research and Development directed toward increasing both the throughput and isotopic purity of the products is also conducted at ORNL. The Isotope Sales Office distributes the isotopes in two ways. Multigram quantities of enriched samples from the Research Materials Collection (RMC) are loaned to members of the DOE research community at a nominal fee for nondestructive research, while enriched isotopes are sold to other research and commercial organizations on a cost-recovery basis.

II. FACILITY DESCRIPTION AND CAPABILITY

The Calutron facility is a unique national asset, since the USSR is the only other nation possessing a similar capability. Many other countries have laboratories where isotopic enhancement is performed, but their facilities are usually of limited size and the isotopes are utilized for specific purposes.

Figure 1 is a schematic drawing of the ORNL facility, which has two "tracks." One track is reserved for stable isotope enrichment, while the other is used to produce radioactive and actinide elements. The horizontal magnetic field of the stable isotope track has been subdivided into four segments by means of magnetic shunts that extend from one side of the track to the other. This subdivision resulted in three banks of eight separators and one bank of six separators. By exciting the magnetic field in each segment independently, it is theoretically possible to enrich the isotopes of four elements simultaneously in the thirty Calutrons.

All of the separators have their source and collectors in the magnetic field. The advantage of this configuration is that it allows a high degree of beam-charge neutralization, and thus high-current densities can be maintained without degrading focal qualities. The disadvantage is that pressure in the entire tank must be brought down to

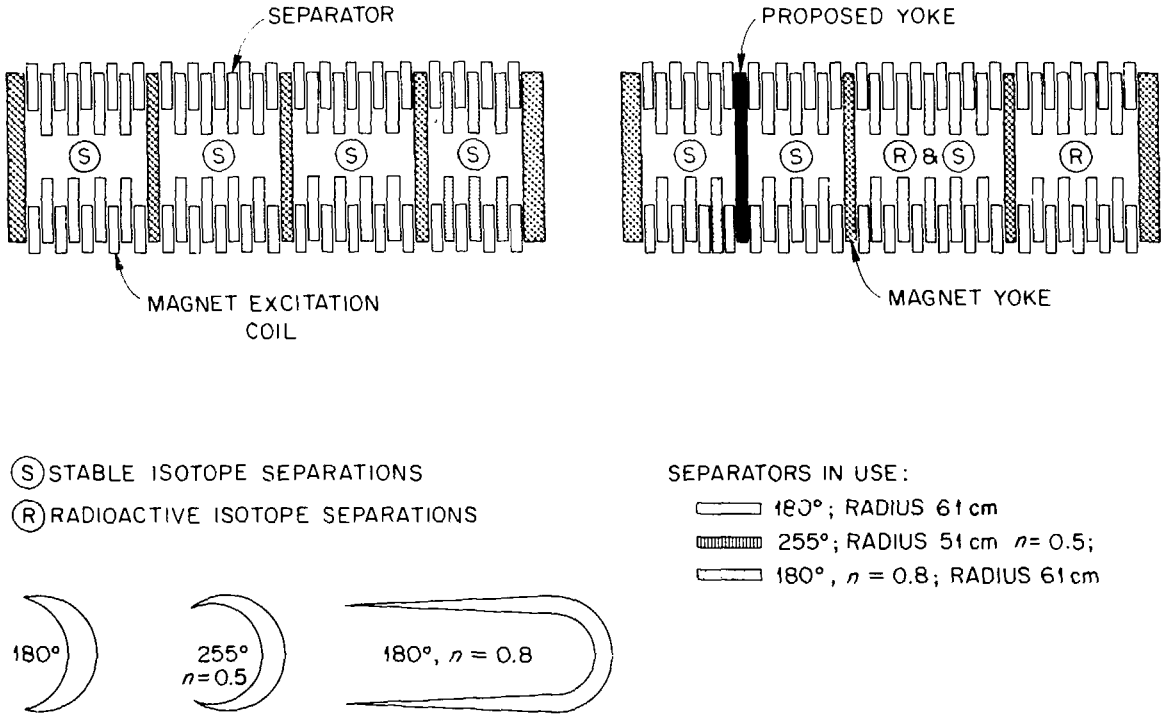

Fig. 1. Schematic plan of the separation facility. The upper blocks represent the two "tracks" of separators and the type of separator in each segment. The geometrical designs depict the beam profile produced by each of the three types of machines.

atmospheric when the source is replenished. Hence, time is spent in reestablishing a high vacuum.

Two types of separators are available for the enrichment of stable isotopes. The first is the standard 180° focusing mass spectrometer; the second is a 255° sector focusing device with a magnetic field index equal to 0.5. Six of the separators are equipped with magnetic pole-faces to give double focusing properties. These six separators have a higher theoretical mass resolution, and their use results in a product with greater isotopic enhancement than the product available from the standard 180° focusing device. The throughput associated with these separators, however, is less than that achieved with the standard Calutron units. In actual practice, the 255° units are used when isotopic assay is the prime consideration, and the 180° units are operated when maximum yield is desired. The actual number of units operated at any one time depends on how much money is available from DOF.

The first step in enrichment is the introduction of feed material, in either elemental or compound form, into a Calutron, where it is either directly vaporized or heated in a stream of carbon tetrahalide to form a volatile halide. This vapor is then introduced into an arc discharge, where it is ionized in the high-current source. The ionized particle is extracted from the ion source, accelerated to approximately 40 keV, and bent in the magnetic field with a radius of curvature of 60 cm. The focused individual isotopic beams are intercepted by collectors, which are constructed of carbon, copper, or aluminum and located behind a slotted face plate. Following a run, whose duration may be between fifty and several hundred hours depending on the element, the collectors are removed from the separator and the material is extracted, chemically purified, assayed, and placed in the inventory.

As might be expected, each element or compound has unique operating characteristics. Thus, it is difficult to make generalizations about the throughput capability of the facility. The ion sources produce a beam whose dimensions are approximately 0.4 x 13 cm. Typical beam currents between 10 and 100 mA are obtained, with the average in the 25-50 mA region. As a rule of thumb, one separator can provide approximately 0.1 mole of an element per operational day. This figure must be multiplied by the natural isotopic abundance to determine the yield for a particular isotope.

It is considerably more difficult to present a universal rule for achievable isotopic purity. Isotopic purity is strongly dependent on the isotope required and the abundance of its nearest neighbors. In addition, the vaporization and ionization characteristics of the element, the probability of the isotope remaining in the collector, and the degree of focusing which can be achieved are all intimately related to the final product assay. With the above considerations clearly in mind, one can approximate the assay by applying a decontamination factor. The ratio of the final assay divided by the tails contamination to the initial assay divided by the feed contamination is given approximately by 23,000 divided by the mass of the isotope. In the lead region, for example, this would yield a decontamination factor on the order of 110. This would mean that an isotope of an initial abundance of 5 percent could be enriched to approximately the 85 percent level in a single pass with a standard 180° Calutron.

The products from one separation can be recycled to obtain a significantly higher isotopic assay in a two-pass process. This is expensive, however, since the efficiency of the process is significantly less than unity. Process efficiency is defined as the ratio of the quantity of material removed from the collectors to the quantity of charge material vaporized. As one might expect, process efficiency is a function of source performance and is typically between 5 and 25 percent, with the average being approximately 10 percent.

Direct production of isotopically enriched surface-deposited targets is also done at the facility. The device used for the preparation of these targets is a 180° sector separator, with the source and collector external to the magnetic field. This device has a dispersion roughly ten times that of the 180° production Calutron unit. Therefore, the isotopic enrichment that can be achieved is significantly greater. The ion throughput is correspondingly lower, however, and while the machine is useful for making special targets, it is not efficient for producing multigram quantities of highly enriched isotopes. In the fabrication of a typical target, the ions are slowed to approximately 200 eV and allowed to impinge on a suitable backing, such as carbon, aluminum, or gold foil. The material is deposited as a line image 1-2 cm x 2 mm, with thicknesses up to approximately 100 $\mu g/cm^2$.

III. INVENTORIES AND DISTRIBUTION

Current DOE policy regarding the Research Materials Collection is that the materials are available on loan to U.S. scientists for use in non-destructive experiments. These materials can also be used in experimental facilities outside the United States, but with restrictions. Among the stipulated conditions are that the experiment must be of relevance to the DOE mission and that the research must be a collaborative effort with a U.S. scientist who has assumed responsibility for the integrity of the sample. There are certain exceptions to this policy, for example, the use of RMC samples within the European community for the study of neutron cross sections. In such cases, the samples are placed in the custody of EURATOM. Such loans are usually made only at the strong recommendation of the European-American Nuclear Data Committee (EANDC).

Materials in the sales inventory, on the other hand, are available to anyone and are sold on a first-come, first-served basis. Although the price and information about the availability of material can be obtained, a sample is sent only upon receipt of a purchase order. This can cause confusion and result in dissatisfaction with the sales operation. A list of the electromagnetically enriched isotopes, their chemical form, percent enrichment, price per mg, and availability as of October 1, 1981, is given in Appendix I. The relative needs of the various users of enriched isotopes offer an interesting picture. The research community utilizes relatively small amounts of almost all the enriched isotopes, while the medical and industrial sectors require large quantities of a very limited number of isotopes. Further, there are isotopes of many elements which are not wanted by anyone. A series of histograms for fiscal years 1970-1980, showing the annual sales

revenues of twenty isotopes, is presented in Appendix II. The rank order is based on the total revenue.

The current inventory is being depleted faster than it is being replenished. Approximately 65 isotopes are totally depleted from the present sales inventory. With a few notable exceptions, these isotopes are needed almost exclusively for research purposes. However, the isotopes for which the demand is greatest are those used in nuclear medical health-care delivery. Obviously, our main concern is to replenish the supplies of these isotopes as rapidly as possible. Accomplishing that will mean that other items in the inventory will be unavailable for some period of time. Requests for special separations of relatively small quantities of material can be accommodated, but the cost is usually greater than that for materials obtained through normal channels. From our viewpoint, the inventory size and associated cost are prime concerns. One must balance efficient production with anticipated demand for a particular isotope. The time needed to provide material through the normal processes is on the order of 6 to 8 months. This is the amount of time required to construct new equipment, prepare for the separation of a particular element, recover the material, and process it to a chemically pure element.

IV. SUMMARY

This paper has attempted to present a brief description of the production of isotopically enriched materials. The ORNL facility used for this purpose suffers from utility and support systems that are rapidly becoming obsolescent and from the fact that the current operational level is insufficient to maintain the sales inventory in equilibrium. The facility does, however, have the equipment and operational capability to almost triple current production. Doubling the number of separators currently in operation, that is, utilizing the full complement of thirty Calutrons in the stable isotope track, would make it possible to restore inventory equilibrium and permit the production of isotopes now out of stock. This increased production could be achieved as rapidly as an expanded operational crew can be trained.

Appendix I

Price and availability of electromagnetically enriched stable isotopes that were available October 1, 1981.

Isotope	Chemical Form	% Enrichment	Price/mg
Antimony -121	Sb	99.46	$ 1.40
Antimony -123	Sb	99.05	1.40
Barium -130	$Ba(NO_3)_2$	37.61	21.25
Barium -132	$Ba(NO_3)_2$	47.99	29.60
Barium -132	$Ba(NO_3)_2$	36.53	17.15
Barium -132	$Ba(NO_3)_2$	21.66	6.05
Barium -134	$Ba(NO_3)_2$	*Material currently not available	
Barium -135	$Ba(NO_3)_2$	56.56	0.55
Barium -136	$Ba(NO_3)_2$	92.90	0.90
Barium -137	$Ba(NO_3)_2$	89.60	0.50
Barium -138	$BaCO_3$	99.67	0.10
Bromine -79	NaBr	98.61	0.75
Bromine -81	NaBr	97.81	0.85
Cadmium -106	CdO	90.80	19.15
Cadmium -106	CdO	80.22	14.95
Cadmium -108	CdO	69.76	18.30
Cadmium -110	CdO	97.20	0.70
Cadmium -110	CdO	96.00	0.65
Cadmium -111	CdO	*Material currently not available	
Cadmium -112	CdO	97.05	0.50
Cadmium -113	CdO	*Material currently not available	
Cadmium -114	CdO	98.55	0.45
Cadmium -116	CdO	*Material currently not available	
Calcium -40	$CaCO_3$	99.96	0.30
Calcium -41	$CaCo_3$	86.50	2,234.65
Calcium -41	$CaCO_3$	63.38	1,199.75
Calcium -41	$CaCO_3$	1.33	0.55
Calcium -42	$CaCO_3$	93.65	6.75

Isotope	Chemical Form	% Enrichment	Price/mg
Calcium -43	$CaCO_3$	*Material currently not available	
Calcium -44	$CaCO_3$	98.68	$ 12.70
Calcium -44	$CaCO_3$	98.55	12.65
Calcium -46	$CaCO_3$	43.35	2,300.20
Calcium -46	$CaCO_3$	34.91	1,491.70
Calcium -48	$CaCO_3$	97.69	167.05
Cerium -136	CeO_2	50.54	76.35
Cerium -136	CeO_2	34.81	36.20
Cerium -138	CeO_2	26.00	27.50
Cerium -140	CeO_2	99.70	0.05
Cerium -142	CeO_2	92.11	1.80
Chlorine -35	NaCl	99.35	0.40
Chlorine -37	NaCl	98.21	7.40
Chromium -50	Cr_2O_3	96.40	5.35
Chromium -52	Cr_2O_3	99.90	0.85
Chromium -53	Cr_2O_3	96.98	2.50
Chromium -54	Cr_2O_3	94.13	13.10
Copper -63	CuO	99.89	0.15
Copper -65	CuO	99.69	0.30
Dysprosium-156	Dy_2O_3	21.59	18.15
Dysprosium-158	Dy_2O_3	20.80	13.00
Dysprosium-160	Dy_2O_3	63.27	1.40
Dysprosium-161	Dy_2O_3	90.41	0.30
Dysprosium-162	Dy_2O_3	92.39	0.30
Dysprosium-163	Dy_2O_3	93.07	0.35
Dysprosium-164	Dy_2O_3	98.43	0.25
Erbium -162	Er_2O_3	27.33	11.90
Erbium -164	Er_2O_3	73.60	2.85
Erbium -166	Er_2O_3	96.24	0.20
Erbium -167	Er_2O_3	91.54	0.25
Erbium -168	Er_2O_3	95.47	0.25
Erbium -170	Er_2O_3	96.89	0.30

Isotope	Chemical Form	% Enrichment	Price/mg
Europium -151	Eu_2O_3	96.83	$ 0.45
Europium -153	Eu_2O_3	94.85	0.45
Gadolinium-152	Gd_2O_3	41.20	19.70
Gadolinium-154	Gd_2O_3	66.53	2.40
Gadolinium-155	Gd_2O_3	91.61	1.75
Gadolinium-155	Gd_2O_3	99.82	6.25
Gadolinium-156	Gd_2O_3	*Material currently not available	
Gadolinium-157	Gd_2O_3	90.96	1.15
Gadolinium-157	Gd_2O_3	99.70	3.35
Gadolinium-158	Gd_2O_3	81.00	0.45
Gadolinium-160	Gd_2O_3	98.71	0.90
Gallium -69	Ga_2O_3	99.46	0.50
Gallium -71	Ga_2O_3	99.80	0.85
Germanium -70	GeO_2	*Material currently not available	
Germanium -72	GeO_2	97.85	0.25
Germanium -73	GeO_2	94.50	6.40
Germanium -74	GeO_2	94.48	0.15
Germanium -76	GeO_2	73.89	5.20
Hafnium -174	HfO_2	19.01	628.10
Hafnium -174	HfO_2	7.87	107.65
Hafnium -176	HfO_2	72.17	15.80
Hafnium -177	HfO_2	86.49	2.40
Hafnium -178	HfO_2	91.94	1.35
Hafnium -179	HfO_2	81.85	1.75
Hafnium -180	HfO_2	93.86	1.35
Indium -113	In_2O_3	96.26	13.15
Indium -115	In_2O_3	99.99	0.50
Iridium -191	Ir	97.13	1.20
Iridium -193	Ir	96.94	0.80
Iron -54	Fe_2O_3	97.08	1.80
Iron -56	Fe_2O_3	99.93	0.10

Isotope	Chemical Form	% Enrichment	Price/mg
Iron -57	Fe_2O_3	90.24	$ 9.00
Iron -57	Fe_2O_3	86.06	8.20
Iron -58	Fe_2O_3	76.54	41.10
Iron -58	Fe_2O_3	73.26	37.65
Iron -58	Fe_2O_3	65.09	29.75
Lanthanum -138	La_2O_3	7.03	40.45
lanthanum -139	La_2O_3	99.99	0.95
Lead -204	$Pb(NO_3)_2$	70.94	5.60
Lead -205	$PbCO_3$	76.75	802.25
Lead -206	$PbCO_3$	99.77	0.95
Lead -207	$Pb(NO_3)_2$	98.22	1.80
Lead -207	$Pb(NO_3)_2$	92.40	0.40
Lead -208	$PbCO_3$	98.69	0.35
Lutetium -175	Lu_2O_3	99.92	0.40
Lutetium -176	Lu_2O_3	*Material currently not available	
Magnesium -24	MgO	99.92	0.35
Magnesium -25	MgO	97.87	2.00
Magnesium -26	MgO	*Material currently not available	
Mercury -196	HgO	47.83	736.85
Mercury -196	HgO	31.84	490.50
Mercury -198	HgO	85.30	10.25
Mercury -199	HgO	85.34	13.30
Mercury -200	HgO	*Material currently not available	
Mercury -201	HgO	*Material currently not available	
Mercury -202	HgO	96.32	15.30
Mercury -204	HgO	*Material currently not available	
Molybdenum-92	Mo	97.37	0.30
Molybdenum-94	Mo	91.59	0.45
Molybdenum-95	Mo	96.47	0.30
Molybdenum-96	Mo	96.76	0.25
Molybdenum-96	Mo	96.44	0.25
Molybdenum-97	Mo	94.25	0.45

Isotope	Chemical Form	% Enrichment	Price/mg
Molybdenum-98	MoO_3	96.90	$ 1.25
Molybdenum-98	Mo	97.18	1.25
Molybdenum-100	Mo	97.42	0.50
Neodymium -142	Nd_2O_3	98.26	1.85
Neodymium -143	Nd_2O_3	91.06	0.80
Neodymium -144	Nd_2O_3	97.51	0.30
Neodymium -145	Nd_2O_3	89.67	1.05
Neodymium -146	Nd_2O_3	97.63	0.45
Neodymium -148	Nd_2O_3	87.90	1.15
Neodymium -150	Nd_2O_3	96.13	1.20
Nickel -58	Ni	99.76	0.35
Nickel -60	Ni	99.07	0.25
Nickel -61	Ni	88.84	14.45
Nickel -61	Ni	86.44	13.70
Nickel -62	Ni	96.64	8.70
Nickel -64	Ni	96.48	16.10
Nickel -64	Ni	93.57	15.15
Nickel -64	Ni	92.16	14.70
Osmium -184	Os	5.45	253.30
Osmium -186	Os	*Material currently not available	
Osmium -187	Os	70.38	23.55
Osmium -188	Os	94.58	3.25
Osmium -189	Os	95.66	2.70
Osmium -190	Os	*Material currently not available	
Osmium -192	Os	*Material currently not available	
Palladium -102	Pd	*Material currently not available	
Palladium -104	Pd	*Material currently not available	
Palladium -105	Pd	*Material currently not available	
Palladium -106	Pd	*Material currently not available	
Palladium -108	Pd	95.29	0.70
Palladium -110	Pd	*Material currently not available	
Platinum -190	Pt	4.19	158.15

Isotope	Chemical Form	% Enrichment	Price/mg
Platinum -192	Pt	57.30	$ 18.30
Platinum -194	Pt	*Material currently not available	
Platinum -195	Pt	*Material currently not available	
Platinum -196	Pt	*Material currently not available	
Platinum -198	Pt	*Material currently not available	
Potassium -39	KCl	99.96	0.30
Potassium -40	KCl	78.88	191.40
Potassium -41	KCl	99.35	6.40
Rhenium -185	Re	96.25	0.60
Rhenium -187	Re	99.22	0.35
Rubidium -85	RbCl	99.78	0.30
Rubdidium -87	RbCl	98.00	3.50
Ruthenium -96	Ru	*Material currently not available	
Ruthenium -99	Ru	*Material currently not available	
Ruthenium -100	Ru	*Material currently not available	
Ruthenium -101	Ru	97.73	1.15
Ruthenium -102	Ru	*Material currently not available	
Ruthenium -104	Ru	96.39	0.90
Samarium -144	Sm_2O_3	*Material currently not available	
Samarium -147	Sm_2O_3	98.34	0.25
Samarium -148	Sm_2O_3	96.40	0.30
Samarium -149	Sm_2O_3	97.60	0.25
Samarium -150	Sm_2O_3	87.27	0.40
Samarium -150	Sm_2O_3	99.93	7.45
Samarium -152	Sm_2O_3	98.29	0.15
Samarium -154	Sm_2O_3	98.69	0.15
Selenium -74	Se	77.71	178.45
Selenium -74	Se	58.19	100.05
Selenium -74	Se	55.91	92.40
Selenium -76	Se	96.88	5.90
Selenium -76	Se	96.06	5.80

Isotope	Chemical Form	% Enrichment	Price/mg
Selenium -77	Se	91.77	$ 10.35
Selenium -78	Se	97.27	4.25
Selenium -80	Se	99.45	0.90
Selenium -82	Se	96.81	29.40
Silicon -28	SiO_2	99.89	0.85
Silicon -29	SiO_2	88.40	2.40
Silicon -30	SiO_2	*Material currently not available	
Silver -107	Ag	98.22	0.40
Silver -109	Ag	99.26	0.60
Strontium -84	$SrCO_3$	99.09	648.05
Strontium -84	$SrCO_3$	97.63	629.10
Strontium -84	$Sr(NO_3)_2$	80.53	51.95
Strontium -86	$SrCO_3$	96.89	0.50
Strontium -87	$Sr(NO_3)_2$	91.15	0.50
Strontium -88	$Sr(NO_3)_2$	99.84	0.15
Strontium -88	$SrCO_3$	99.84	0.15
Sulfur -32	S	99.86	0.45
Sulfur -33	S	59.15	31.30
Sulfur -33	S	48.56	21.10
Sulfur -34	S	94.33	3.25
Sulfur -36	S	1.50	78.05
Tantalum -180	Ta_2O_5	4.10	887.35
Tellurium -120	Te	51.38	156.75
Tellurium -122	Te	96.45	24.00
Tellurium -123	Te	89.39	37.40
Tellurium -123	Te	85.40	34.10
Tellurium -124	Te	96.17	10.17
Tellurium -125	Te	95.67	2.25
Tellurium -126	Te	98.69	0.30
Tellurium -128	Te	99.19	0.20
Tellurium -130	Te	99.29	0.20

Isotope	Chemical Form	% Enrichment	Price/mg
Thallium -203	Tl_2O_3	96.14	$ 1.76
Thallium -203	Tl_2O_3	95.60	1.74
Thallium -205	Tl_2O_3	99.44	0.45
Tin -112	SnO_2	80.04	19.35
Tin -114	SnO_2	64.12	15.05
Tin -115	SnO_2	32.43	93.45
Tin -116	SnO_2	95.60	0.35
Tin -117	SnO_2	84.23	0.35
Tin -118	SnO_2	97.79	1.15
Tin -119	SnO_2	84.48	0.30
Tin -120	SnO_2	98.39	0.40
Tin -122	SnO_2	92.20	0.70
Tin -124	SnO_2	96.71	0.55
Titanium -46	TiO_2	81.20	1.10
Titanium -47	TiO_2	82.75	1.25
Titanium -48	TiO_2	99.65	0.30
Titanium -49	TiO_2	76.27	1.45
Titanium -50	TiO_2	68.09	1.60
Tungsten -180	WO_3	8.76	9.05
Tungsten -182	WO_3	94.40	0.30
Tungsten -183	WO_3	82.50	0.35
Tungsten -184	WO_3	94.80	0.35
Tungsten -186	WO_3	*Material currently not available	
Ytterbium -168	Yb_2O_3	*Material currently not available	
Ytterbium -170	Yb_2O_3	78.78	6.85
Ytterbium -171	Yb_2O_3	95.07	0.55
Ytterbium -172	Yb_2O_3	97.15	0.40
Ytterbium -173	Yb_2O_3	92.08	0.40
Ytterbium -174	Yb_2O_3	98.97	0.25
Ytterbium -176	Yb_2O_3	96.68	0.35
Vanadium -50	V_2O_5	36.00	121.15

Isotope	Chemical Form	% Enrichment	Price/mg
Zinc -64	ZnO	99.69	$ 0.45
Zinc -66	ZnO	98.22	0.65
Zinc -67	ZnO	93.11	4.15
Zinc -67	ZnO	89.68	3.85
Zinc -68	ZnO	99.34	2.17
Zinc -70	ZnO	*Material currently not available	
Zirconium -90	ZrO_2	99.36	0.95
Zirconium -91	ZrO_2	94.59	15.15
Zirconium -92	ZrO_2	98.06	1.70
Zirconium -94	ZrO_2	98.58	5.00
Zirconium -96	ZrO_2	95.63	82.85

*A new separation for some of the items listed as "currently not available," and for items currently in inventory, will be made within the next three years. Items for which a separation is not scheduled may be supplied from a special separation. The costs for these materials will be considerably higher and the delivery dates need to be negotiated. Should you be interested, provide us with the quantity and enrichment of the isotope desired and we will provide you with an estimate of costs and availability.

ORNL DWG 81-783

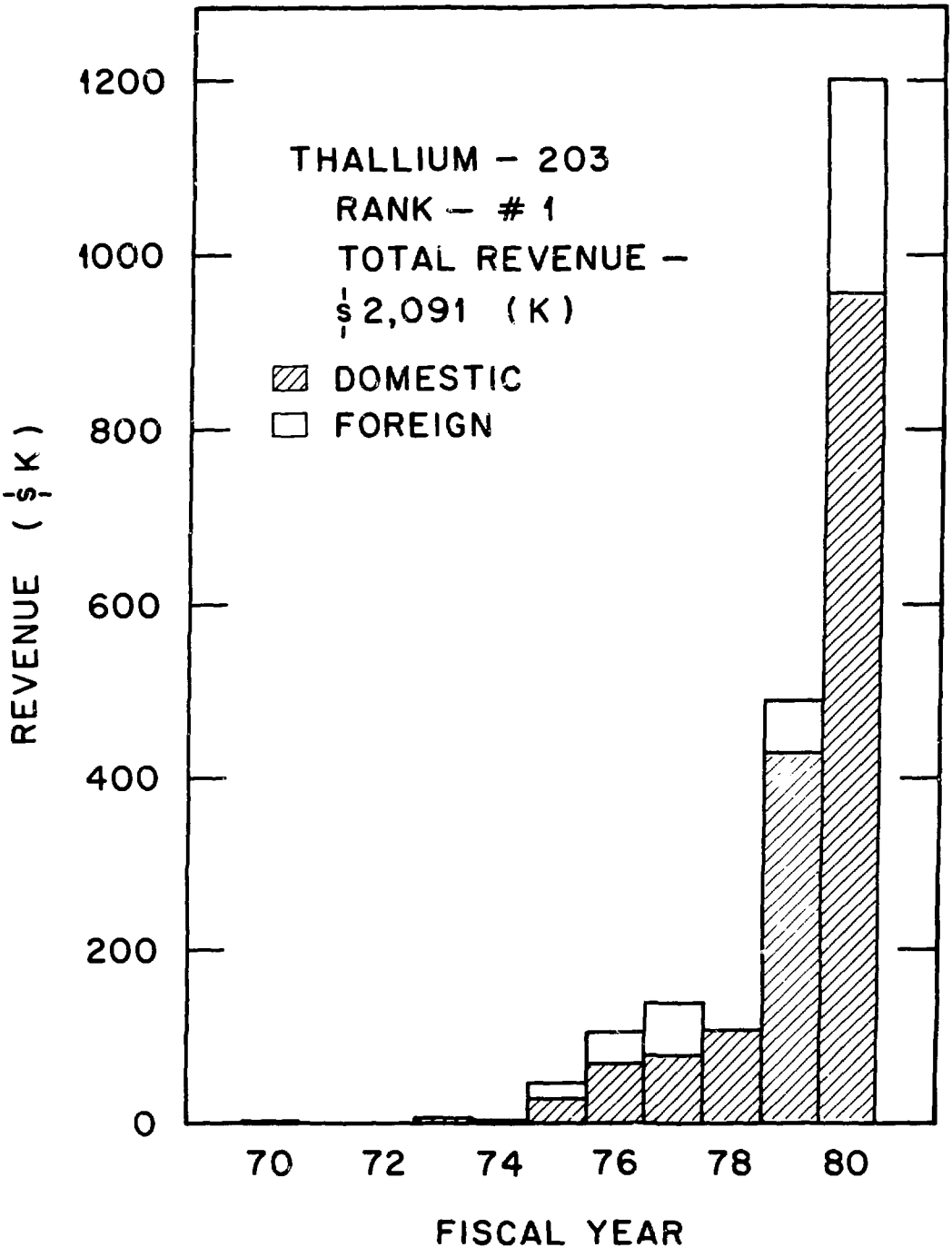

FIGURE 1.

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ORNL DWG 81-836

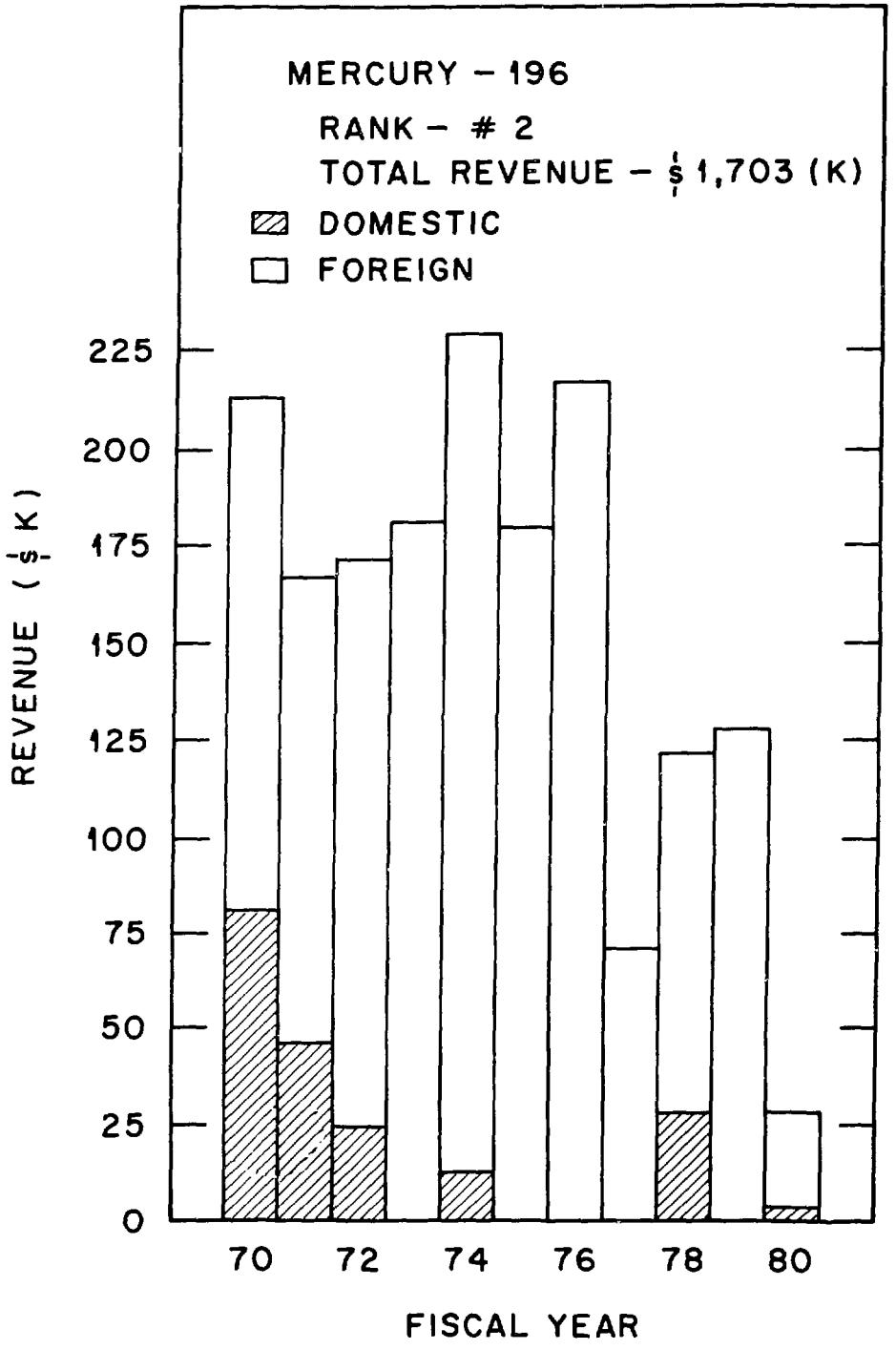

FIGURE 2

ornl

ORNL DWG 81-835

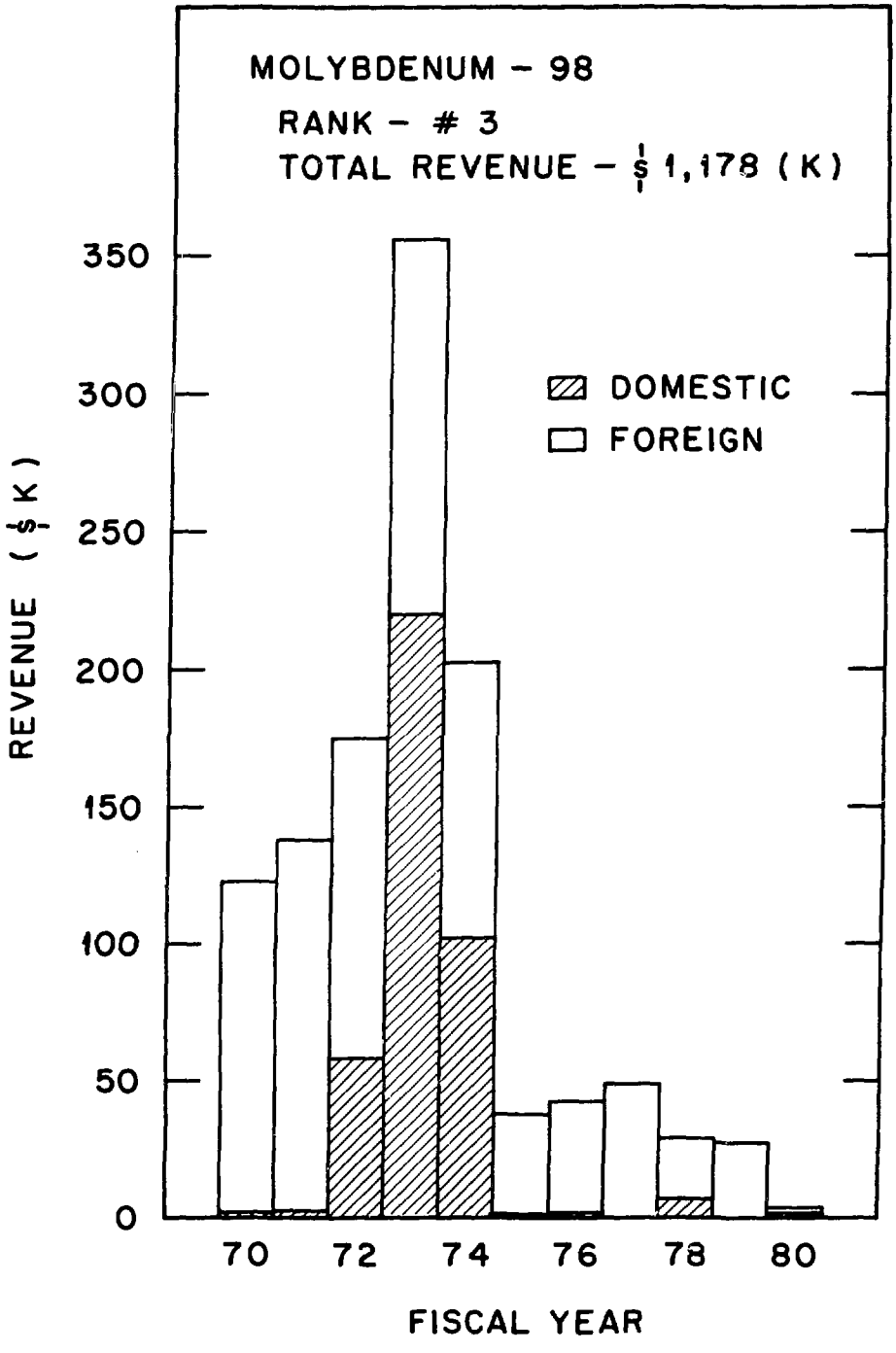

FIGURE 3

ornl

ORNL DWG 81-795

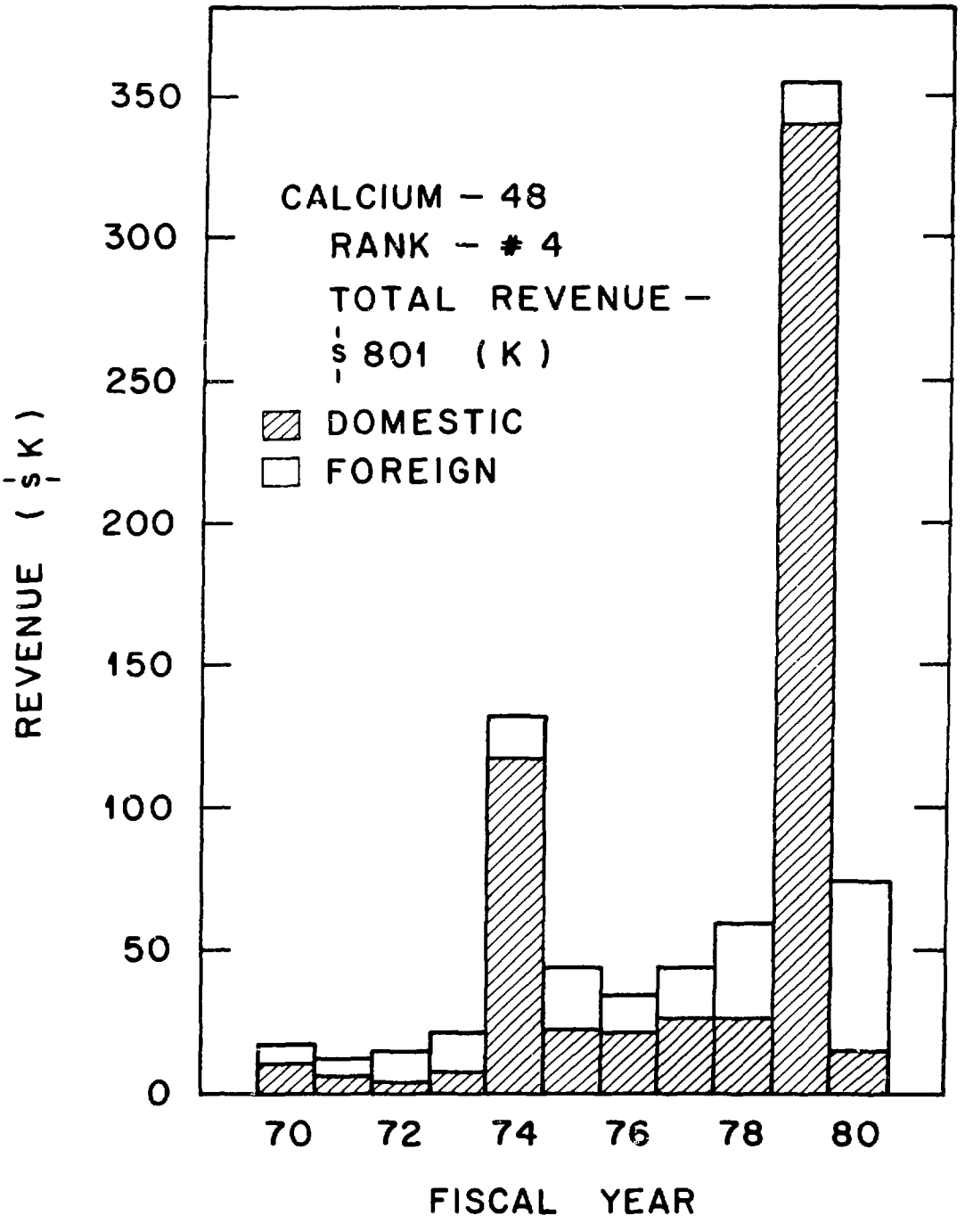

FIGURE 4

ornl

ORNL DWG 81-798

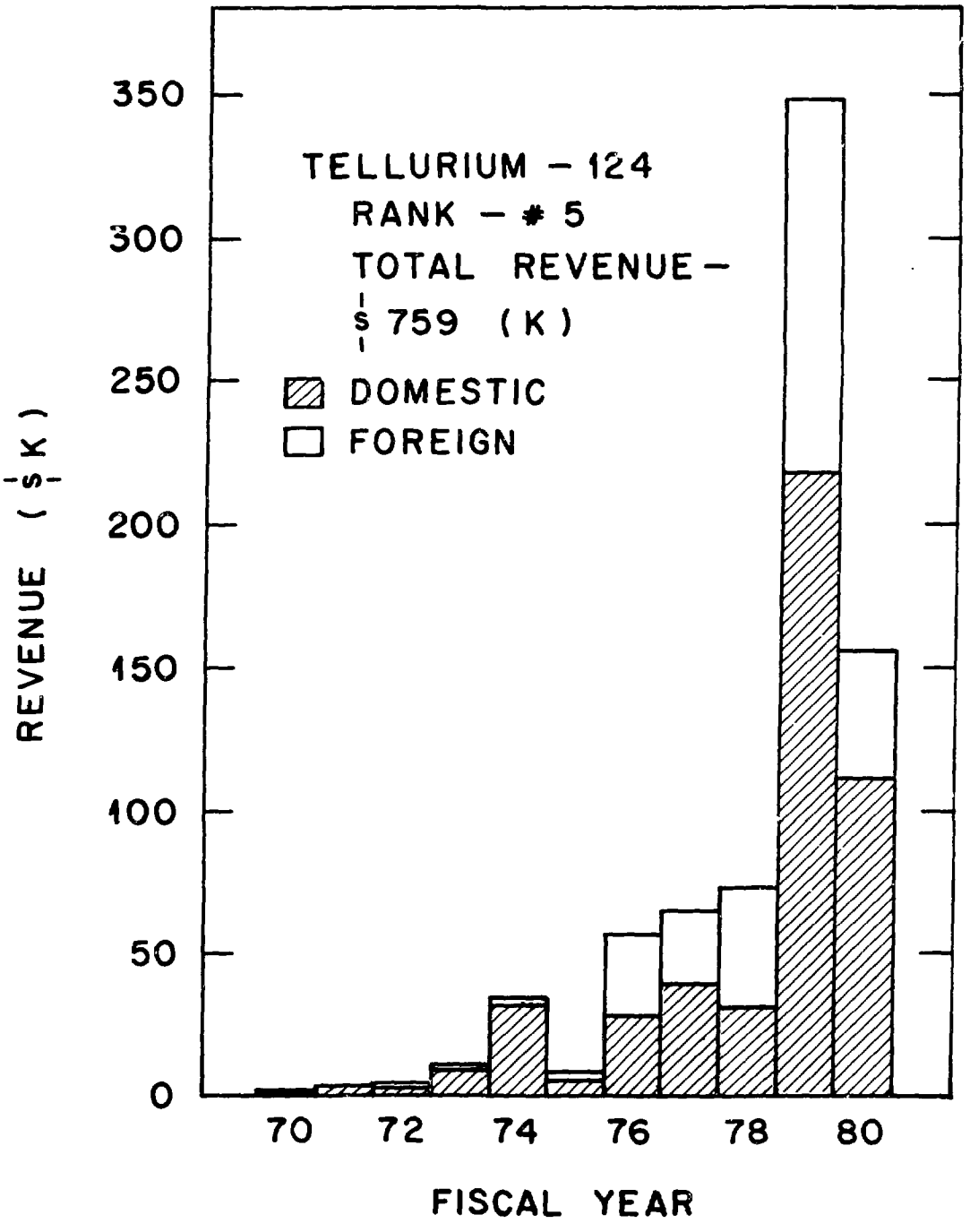

FIGURE 5

ornl

ORNL DWG 81-839

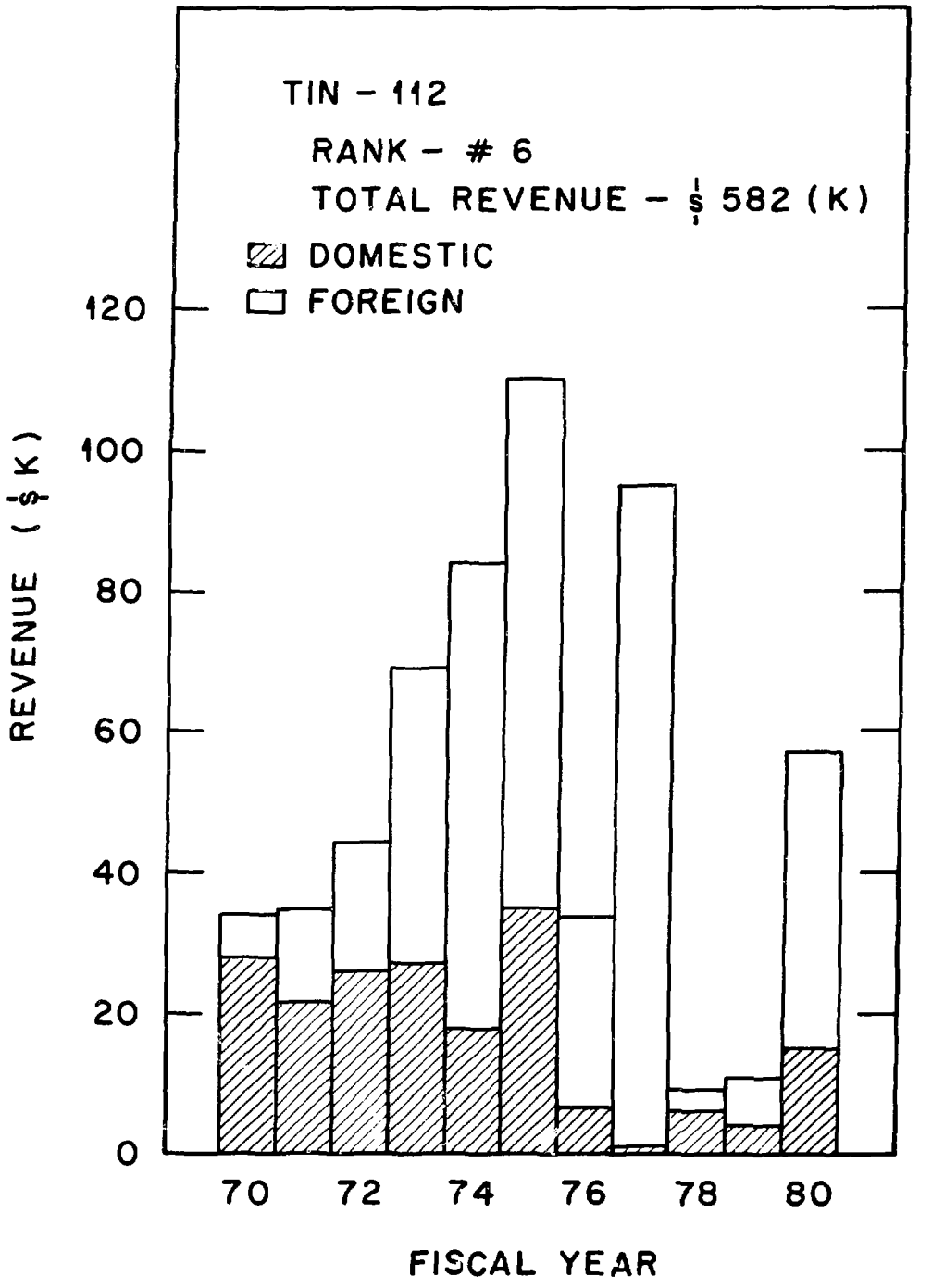

FIGURE 6

ornl

ORNL DWG 81-805

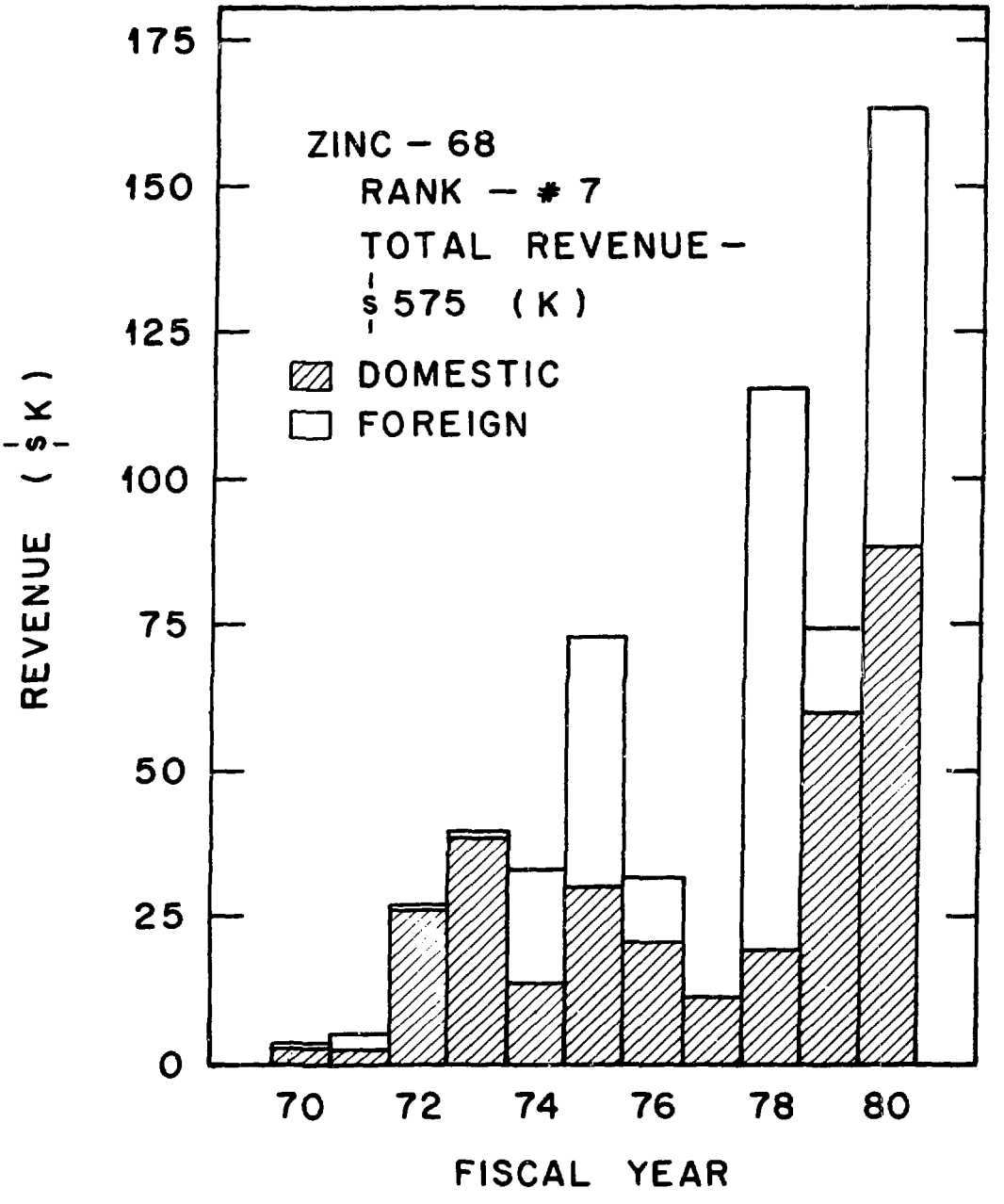

FIGURE 7

ornl

ORNL DWG 81-838

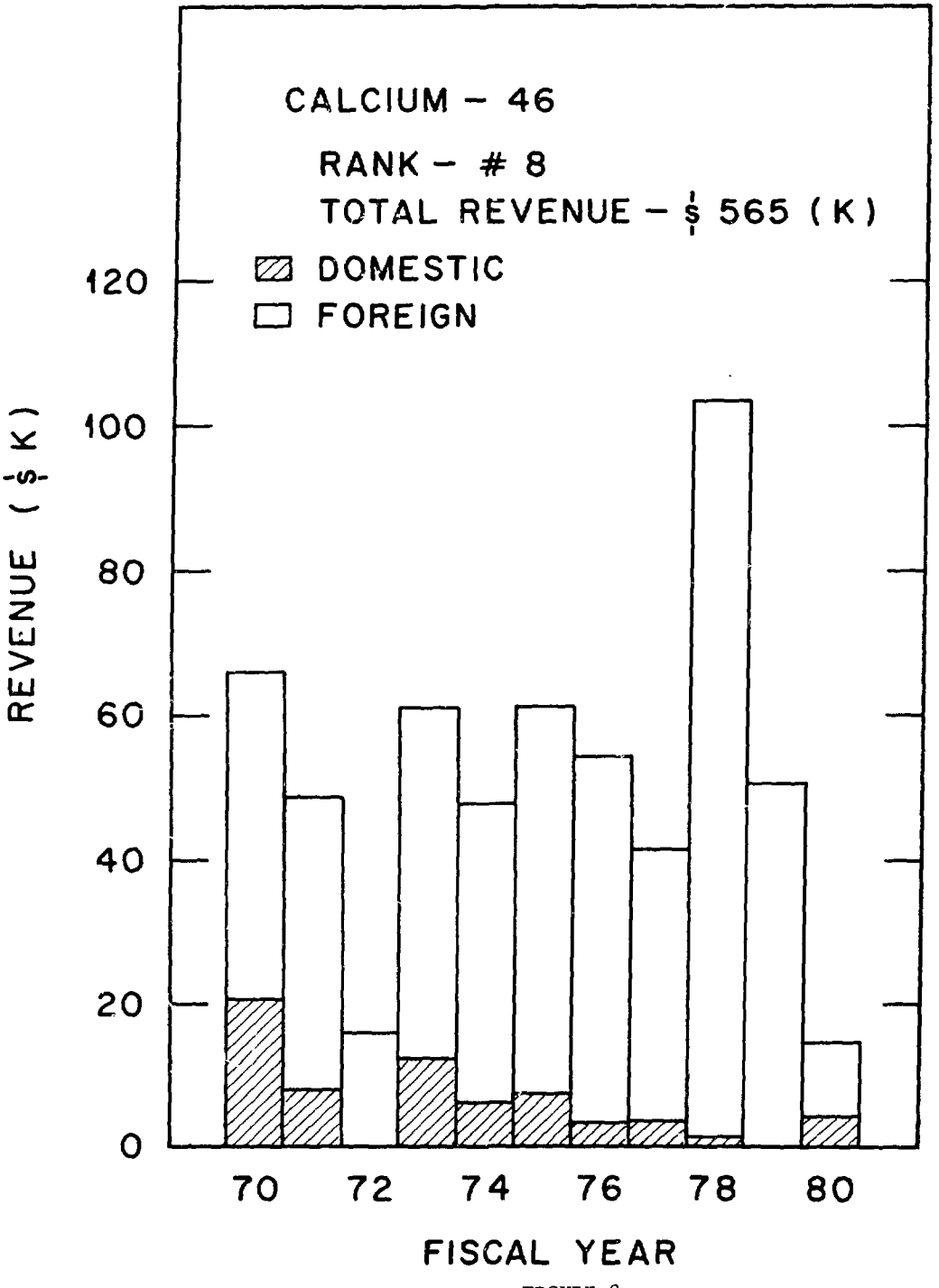

FIGURE 8

ornl

ORNL DWG 81-834

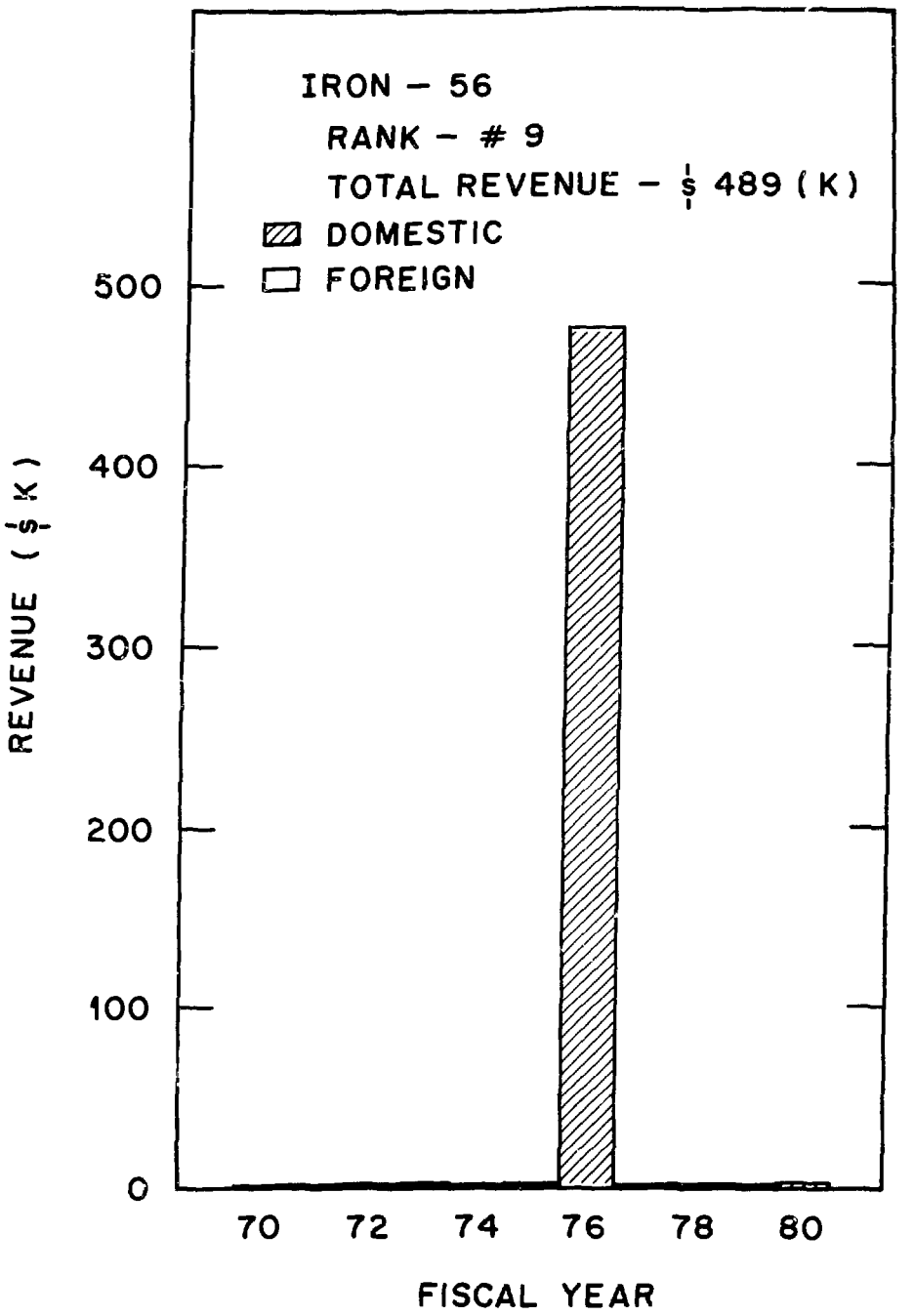

FIGURE 9

ornl

ORNL DWG 81-806

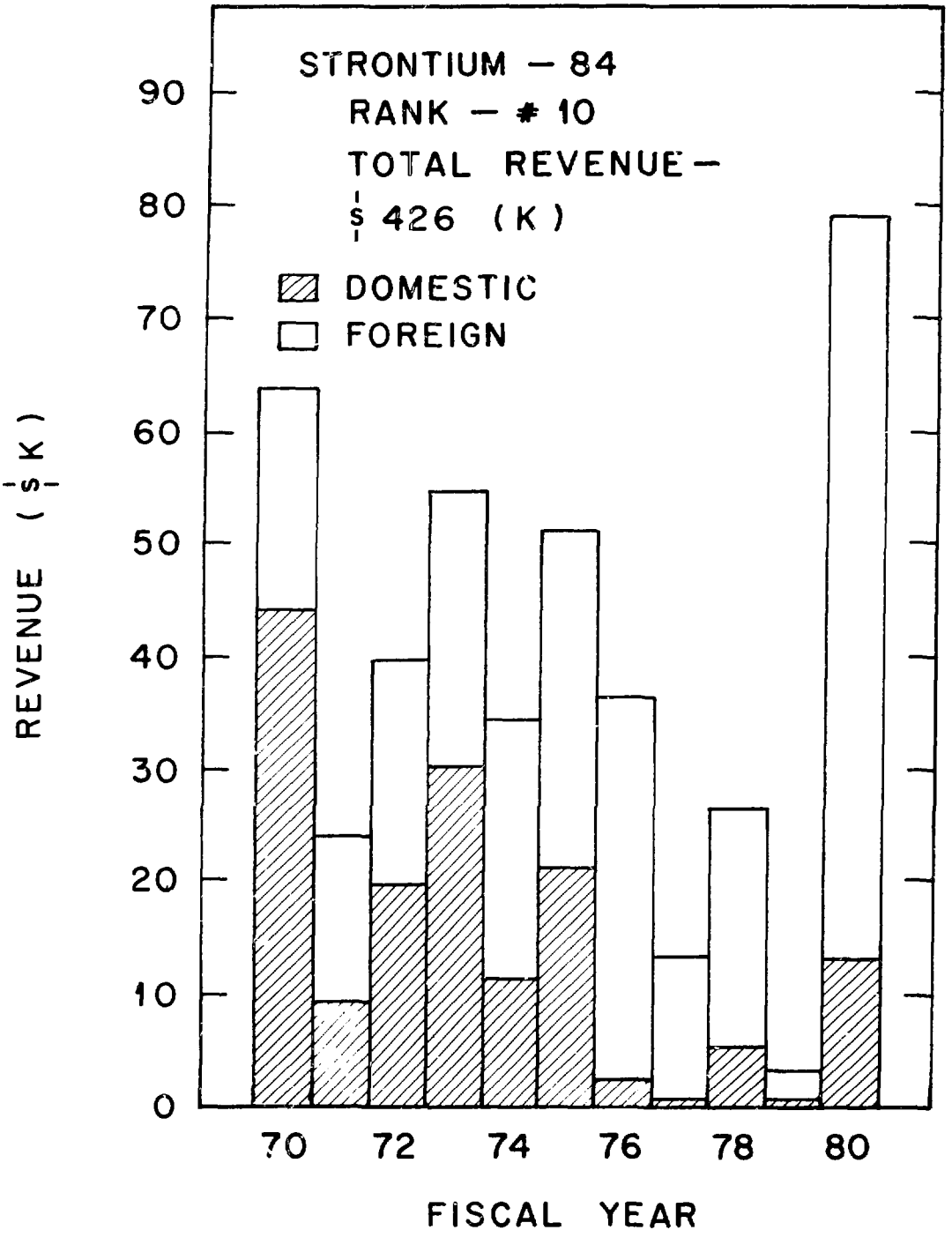

FIGURE 10

ornl

ORNL DWG 81-864

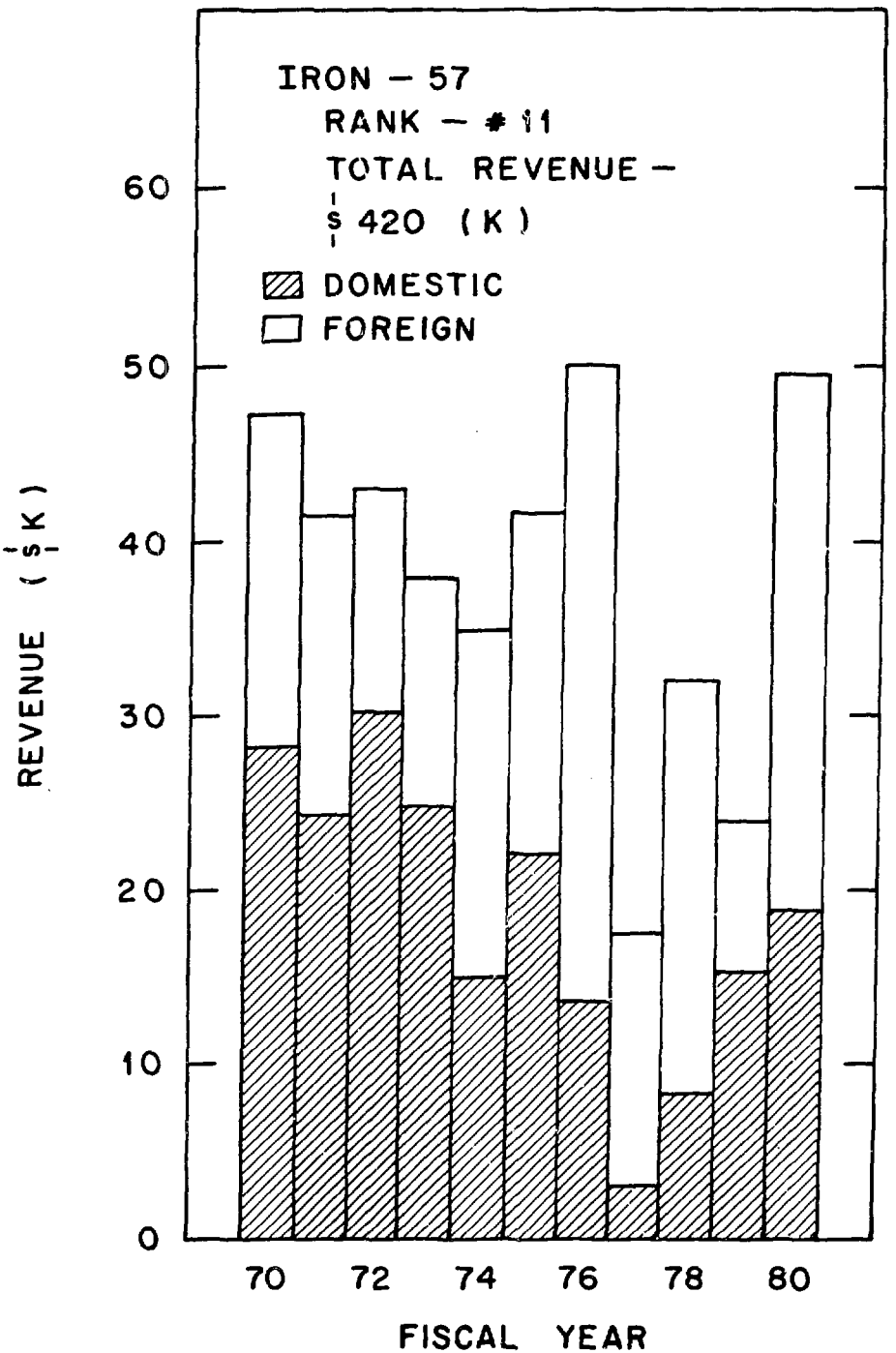

FIGURE 11

ORNL DWG 81-837

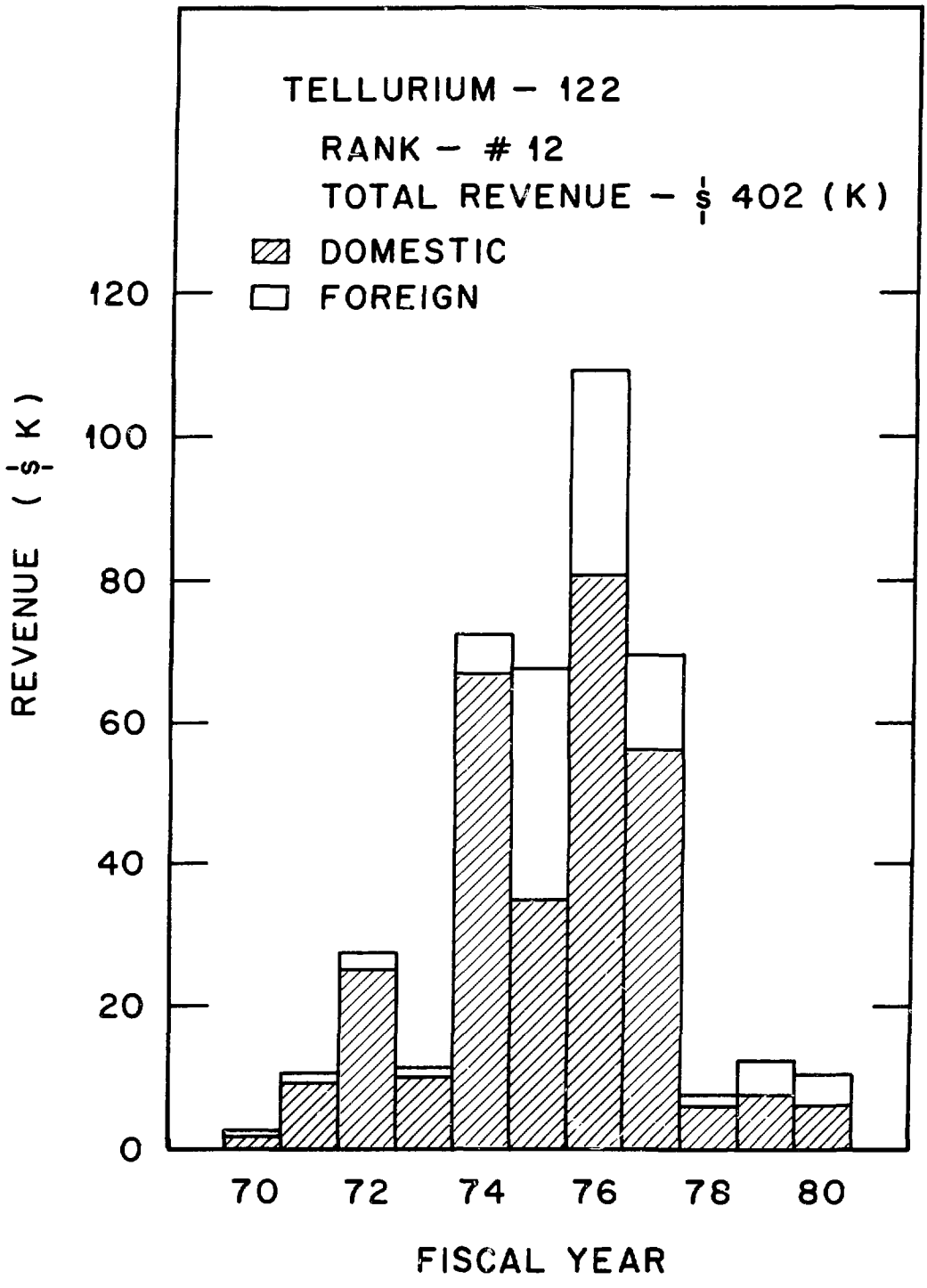

FIGURE 12

ornl

ORNL DWG 81-797

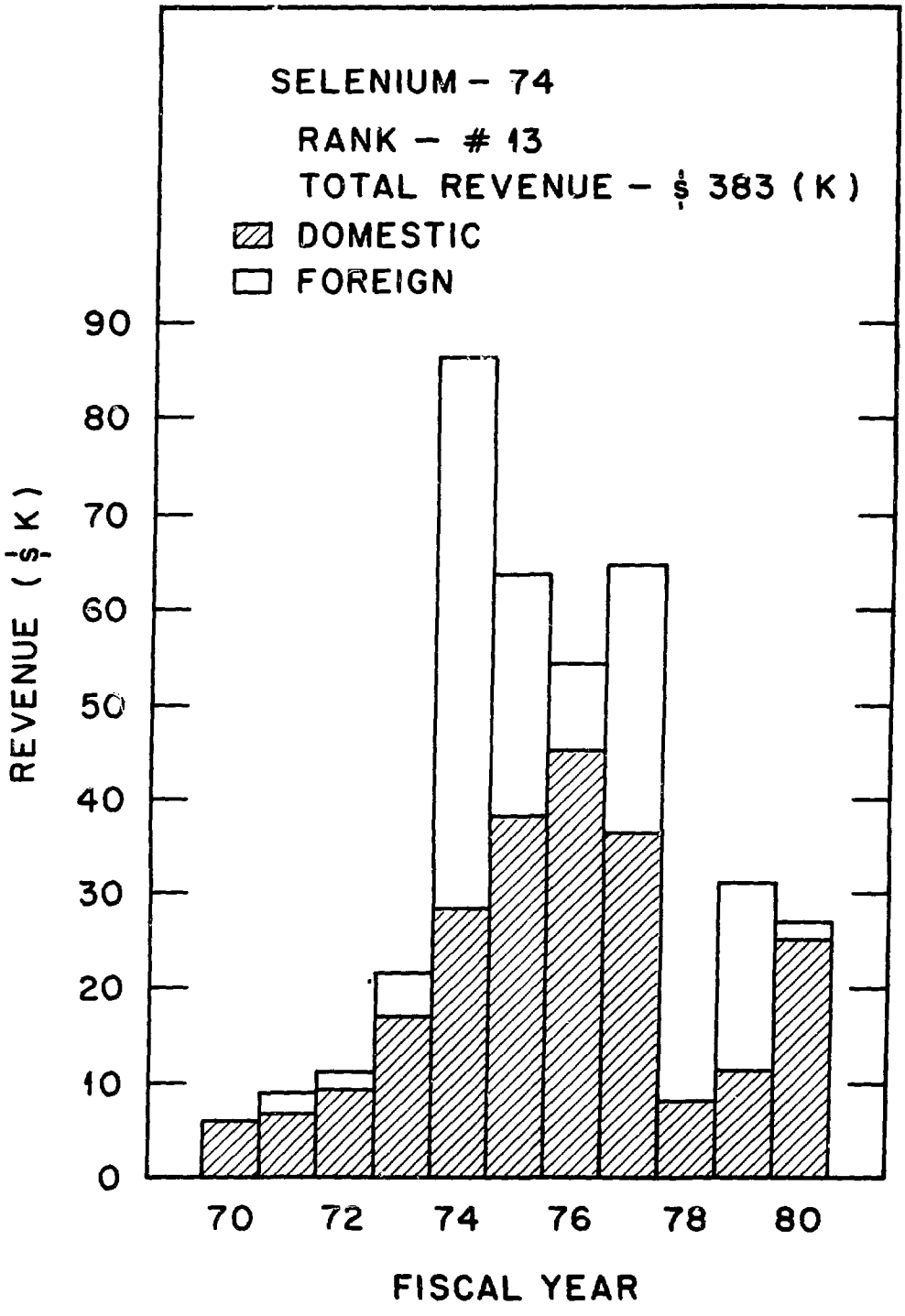

FIGURE 13

ornl

ORNL DWG 81 – 796

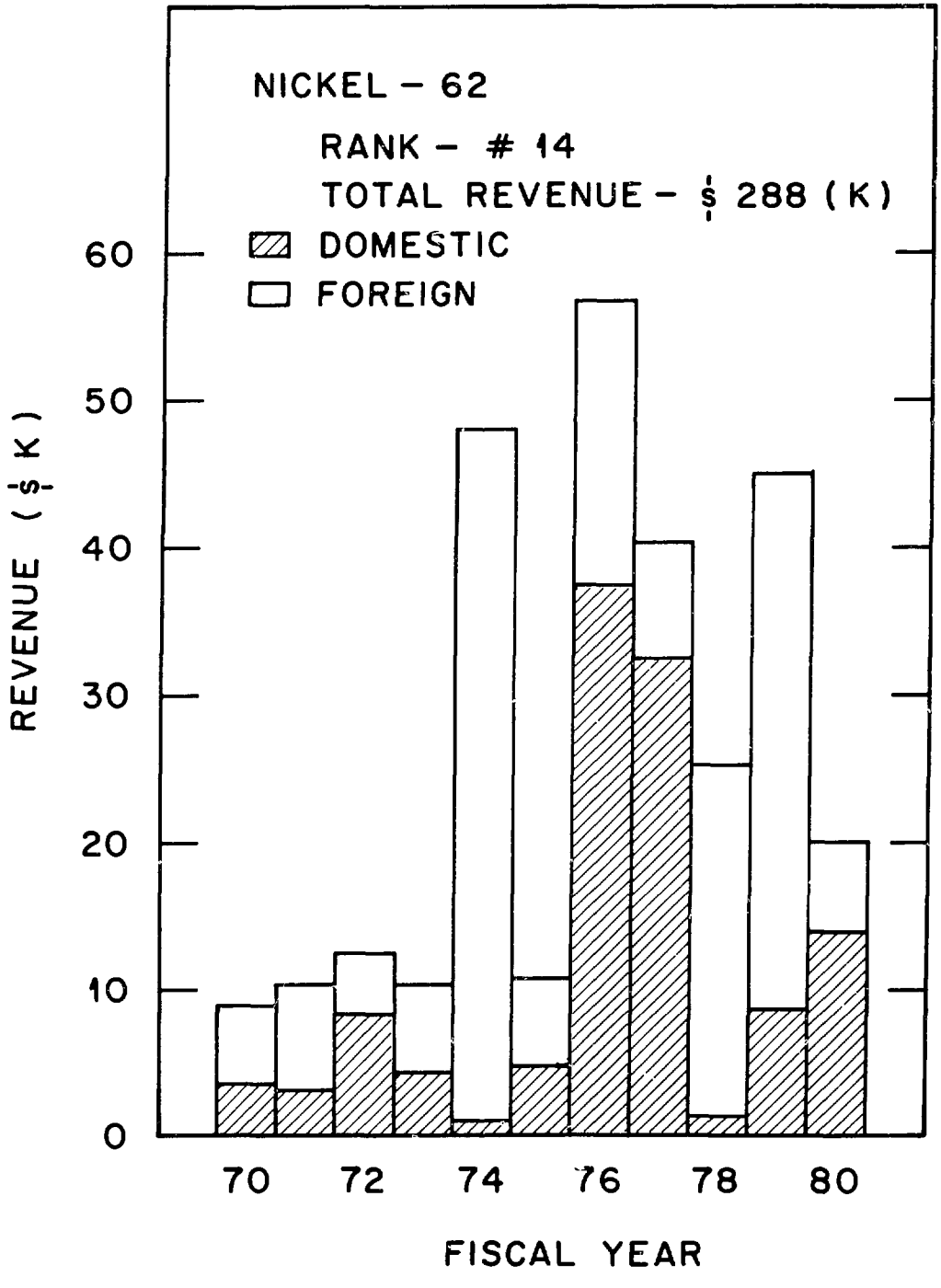

FIGURE 14

ornl

ORNL DWG 81-863

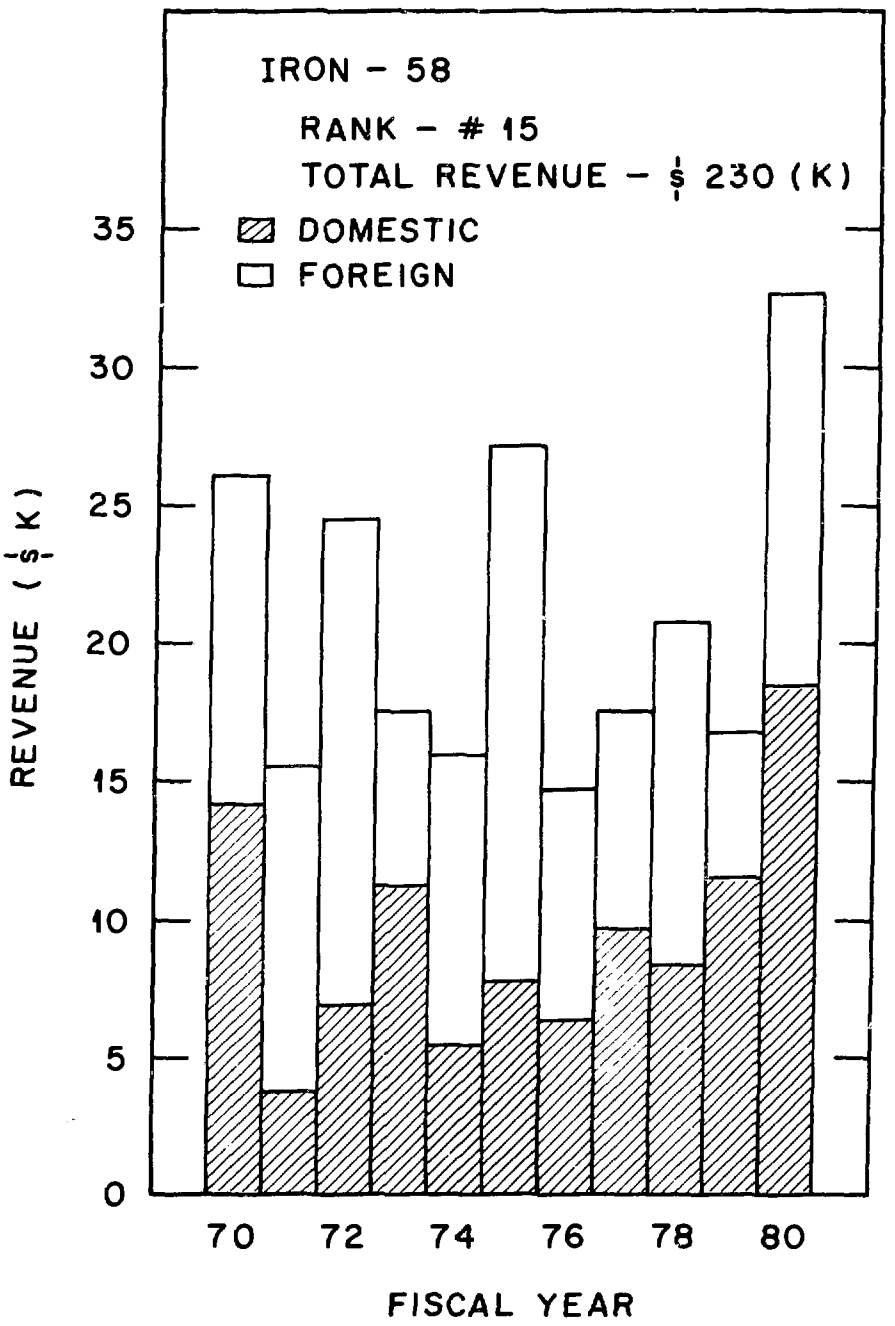

FIGURE 15

ornl

ORNL DWG 81-785

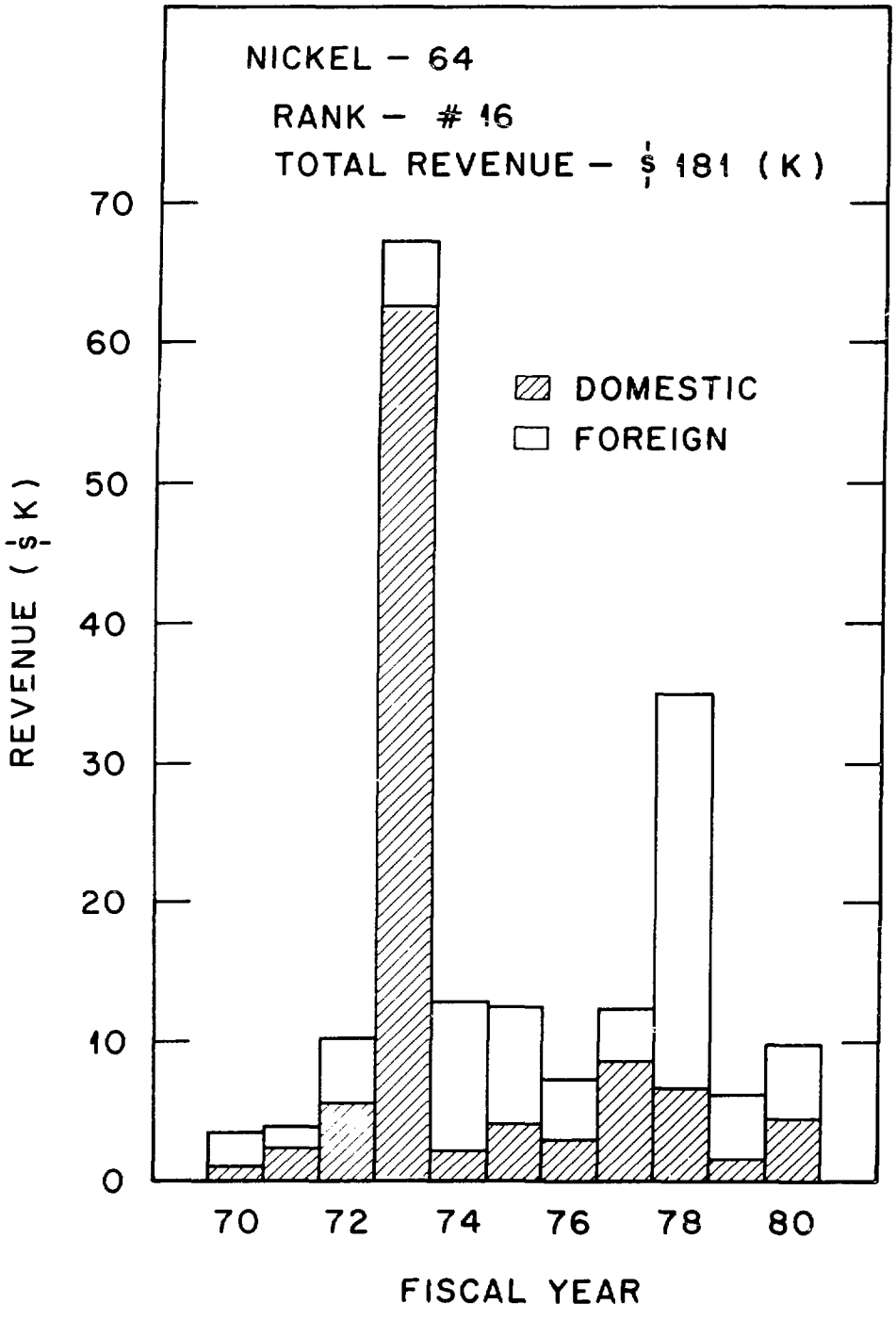

FIGURE 16

ornl

ORNL DWG 81-786

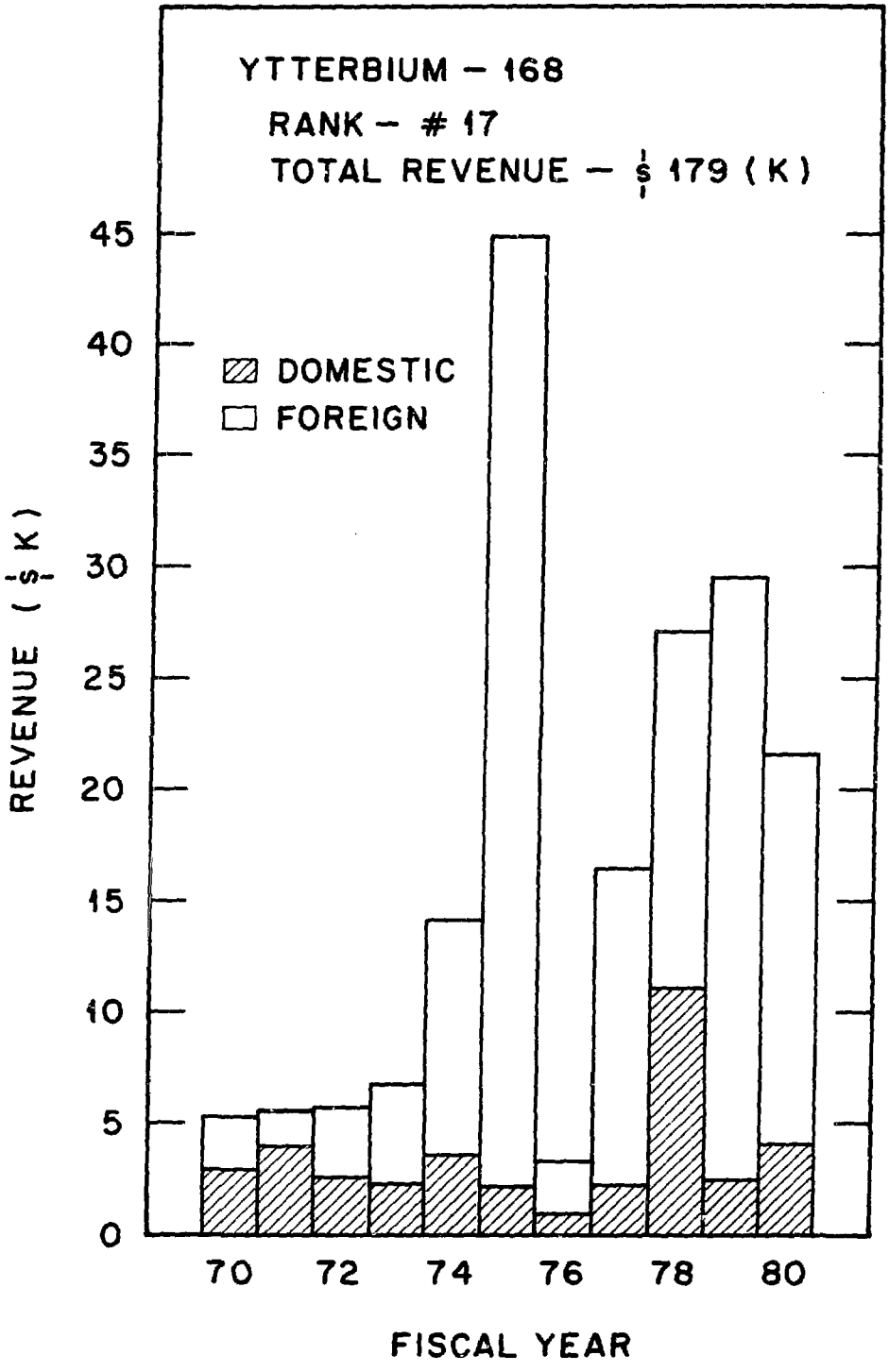

FIGURE 17

ornl

ORNL DWG 81-800

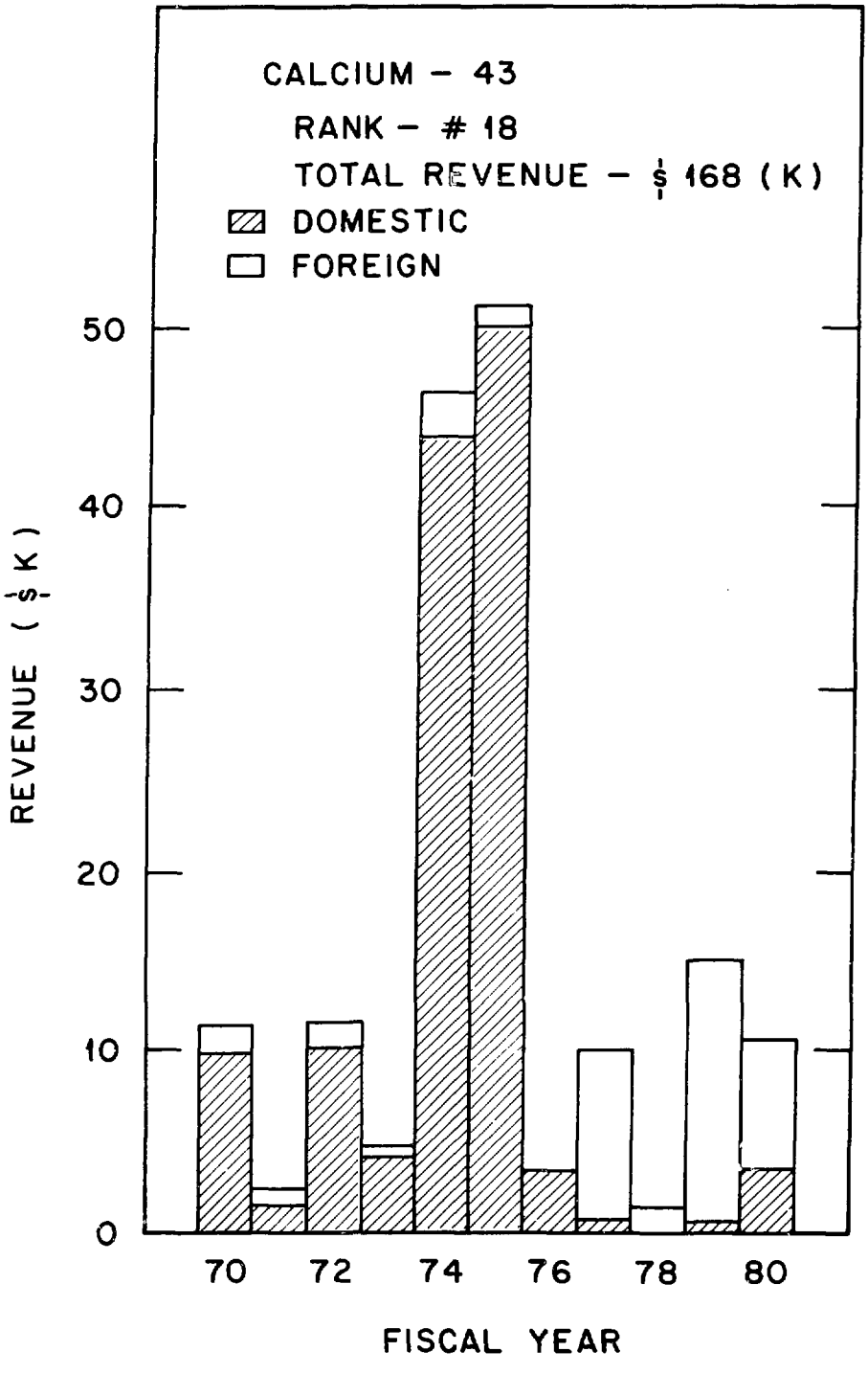

FIGURE 18

ornl

ORNL DWG 81-801

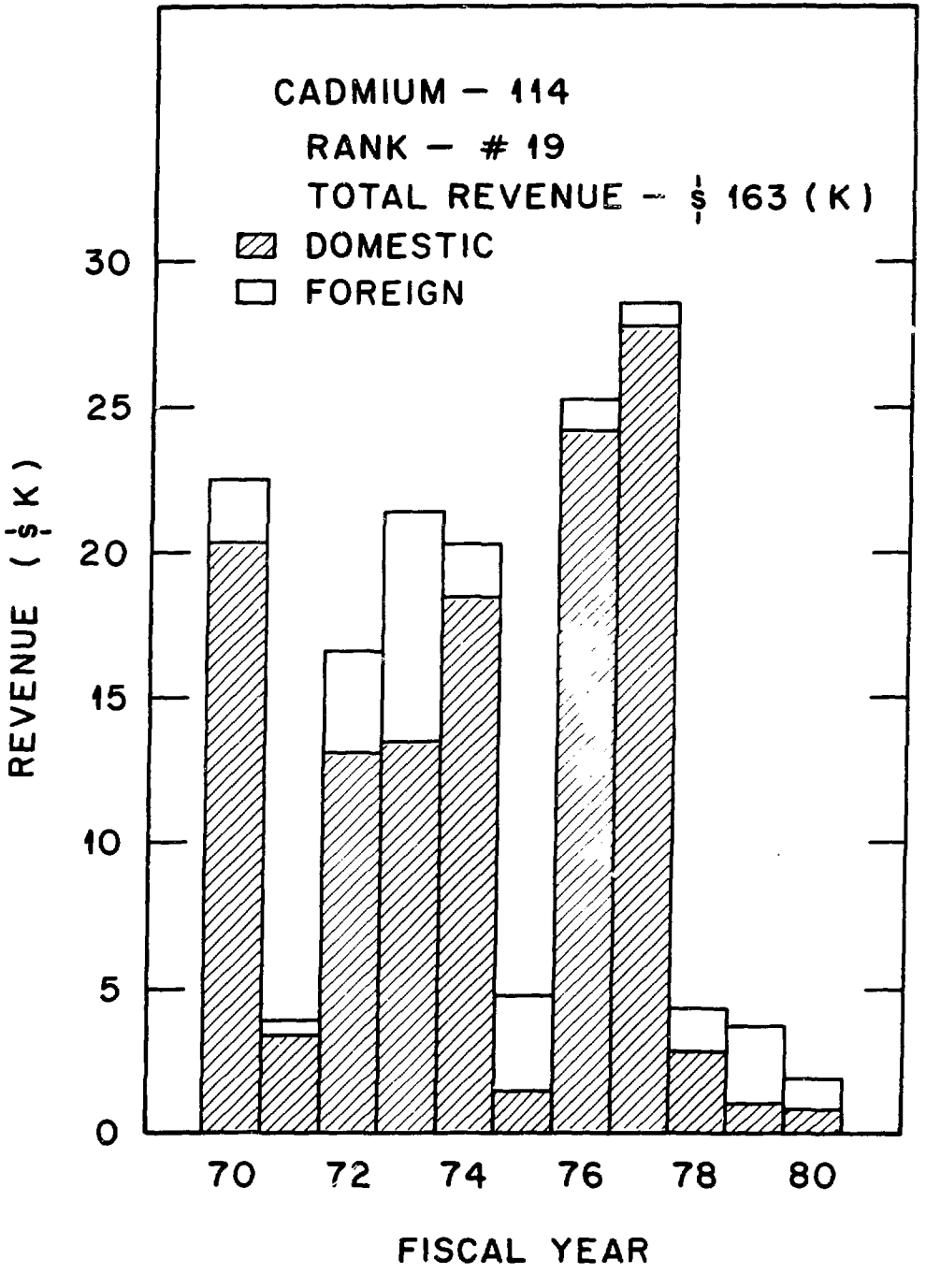

FIGURE 19

ornl

ORNL DWG 81-784

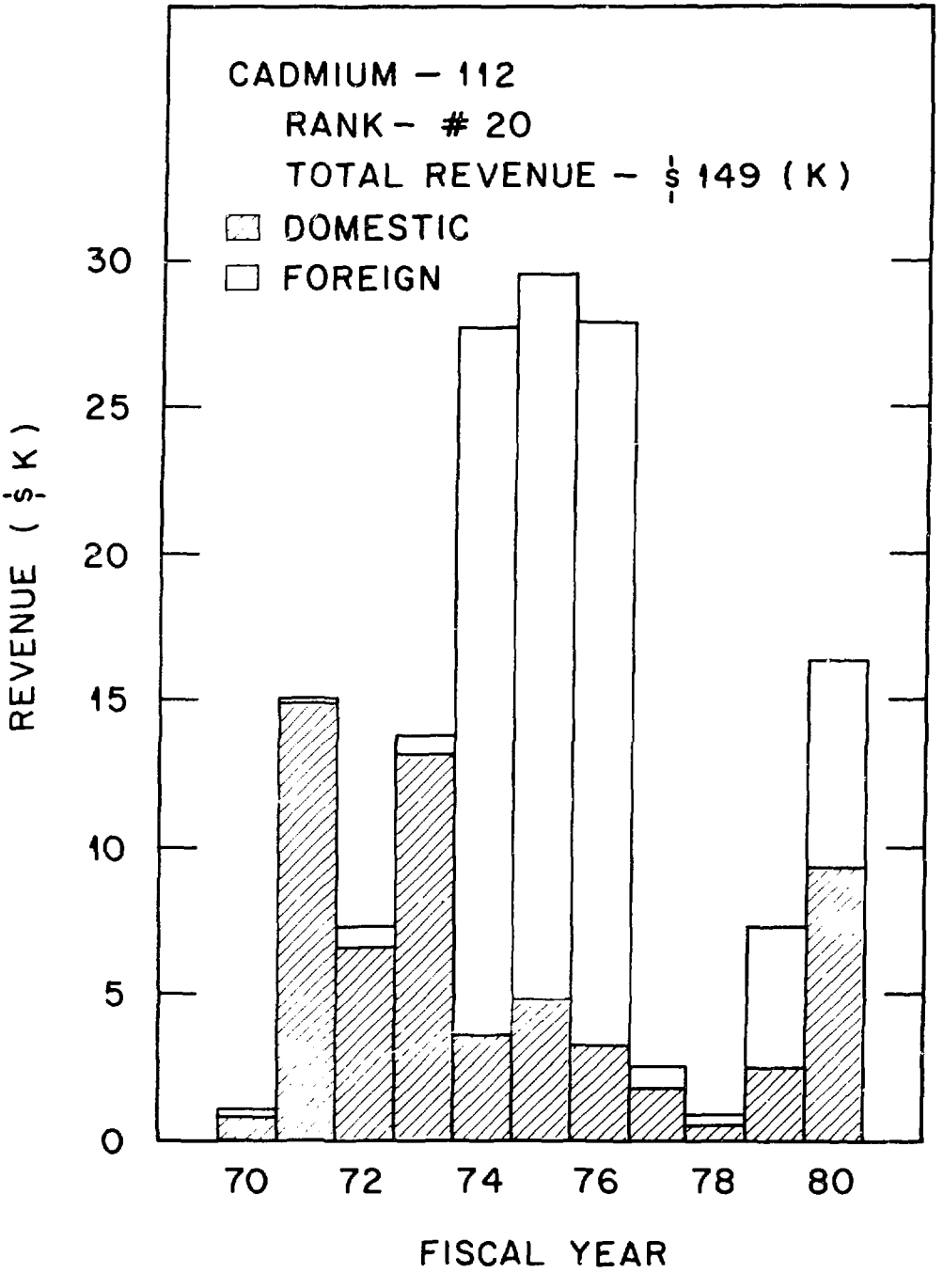

FIGURE 20

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Appendix II

Sales revenue for fiscal years 1970-1980 for twenty electromagnetically enriched isotopes. The ranking is based on the total revenue.

Rank	Isotope	$ 1970-1980 11-Year Total
1	Tl-203	$ 2,090,879
2	Hg-196	1,702,859
3	Mo-98	1,177,798
4	Ca-48	800,742
5	Te-124	758,553
6	Sn-112	581,797
7	Zn-68	575,145
8	Ca-46	564,751
9	Fe-56	488,616
10	Sr-84	425,727
11	Fe-57	420,059
12	Te-122	401,893
13	Se-74	382,896
14	Ni-62	288,072
15	Fe-58	229,495
16	Ni-64	181,010
17	Yb-168	178,591
18	Ca-43	168,136
19	Cd-114	162,913
20	Cd-112	149,134
	TOTAL	$11,729,066

APPENDIX 5

NATIONAL USES AND NEEDS FOR SEPARATED STABLE ISOTOPES IN PHYSICS, CHEMISTRY, AND GEOSCIENCE RESEARCH

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January, 1982

Abstract

Present uses of separated stable isotopes in the fields of physics, chemistry, and the geosciences have been surveyed to identify current supply problems and to determine future needs. Demand for separated isotopes remains strong, with 220 different nuclides having been used in the past three years. The largest needs, in terms of both quantity and variety of isotopes, are found in nuclear physics research. Current problems include a lack of availability of many nuclides, unsatisfactory enrichment of rare species, and prohibitively high costs for certain important isotopes. It is expected that demands for separated isotopes will remain roughly at present levels, although there will be a shift toward more requests for highly enriched rare isotopes. Significantly greater use will be made of neutron-rich nuclides below A=100 for producing exotic ion beams at various accelerators. Use of transition metal nuclei for nuclear magnetic resonance spectroscopy will expand. In addition, calibration standards will be required for the newer techniques of radiological dating, such as the Sm/Nd and Lu/Hf methods, but in relatively small quantities. Most members of the research community would be willing to pay considerably more than they do now to maintain adequate supplies of stable isotopes.

I. INTRODUCTION

In this document we will enumerate the present and future needs for separated stable isotopes, and the uses to which they are being (or will be) put, in physical and chemical research. Other authors will discuss biomedical, clinical, and industrial uses of stable isotopes. This information is especially relevant now, since problems have recently arisen which are beginning to impact the availability of such isotopes. In particular, supplies of many isotopes separated electromagnetically at the Oak Ridge National Laboratory (ORNL) have been exhausted, costs of new supplies have increased enormously, and the ORNL separators (calutrons) are beginning to feel their age.

Since World War II the basic research community, particularly in the field of nuclear physics, has provided the raison d'etre for having a substantial capability to separate isotopes in this country. This is true in the sense that nuclear physicists require a very broad range of separated isotope materials; at one time or another, separated isotopes of nearly all stable elements have been (and continue to be) used in nuclear physics research. Such diverse needs are not surprising, since the particular effects and properties which are of interest to nuclear physicists depend on the specific nucleus being studied, and can change drastically as a result of the addition or removal of even a single nucleon. Thus, investigating nuclear properties without separated isotope materials would be analogous to studying chemical reactions with impure reagents -- it becomes difficult, perhaps impossible, to correlate the observed effects with particular properties of the system under study.

[Of course, certain elements are mono-isotopic, but these constitute only 20 of the 280 stable isotopes. Many of them are utilized in physical and chemical research, but they will not be emphasized here since they require no separation. Furthermore, we will not discuss the needs and uses for gaseous isotopes, such as ^{3}He, or the relatively common radioactive sources, such as ^{252}Cf, ^{148}Gd, ^{57}Co, ^{22}Na, etc. These omissions should not be taken to reflect a lack of importance in either case. The use of ^{3}He for achieving very low temperatures ($<1^{0}$ K) is an extremely interesting topic, and even the lowly radioactive sources play a critical role in scientific endeavors ranging from undergraduate teaching at one extreme to calibrating detectors for high energy physics experiments and space shots at the other.]

While it is generally true that research scientists require a great variety of separated isotope materials, the quantities used by an individual researcher are rather modest, usually on the order of 10 to 1000 mg per year for each isotope. This is in contrast to the more "applied" uses of separated isotopes, where the tendency is to utilize a relatively few isotopes in rather large quantities. Maintaining a supply of a few high-demand items is clearly a more economical proposition than maintaining many different isotopically separated materials in moderate amounts. This is the problem which the research community is now facing.

To get an overview of the existing situation with regard to usage of stable isotopes by researchers in the United States, a questionnaire (see Appendix A) was sent to more than 1,000 physics and chemistry departments nationally, including both academic institutions and national laboratories. A list of the institutions contacted is provided in Appendix B; the names of those scientists responding to the survey are listed in Appendix C. Altogether, 231 institutions responded to this request for information, and 553 completed questionnaires were returned. Considering the length of the questionnaire, the number of respondents alone speaks eloquently for the importance the research community attaches to having a steady supply of separated isotopes.

Based on the responses, the research areas relevant to this report with significant requirements for separated stable isotopes are:

(1) Nuclear Physics/Chemistry
(2) Medium Energy Physics
(3) Radiochemistry
(4) Other Chemistry (Physical, Inorganic, Analytical)
(5) Other Physics (Atomic, Solid State)
(6) Geosciences

In Sec. II the separated isotope requirements for each of these areas will be indicated, along with examples of the uses to which the material is put. Of necessity, the selection of examples will not be complete, but should at least give some overview of recent work in the various fields. Problems associated with the present supplies of isotopes will be described in Sec. III, and Sec. IV will discuss trends in future requirements in these research areas. Finally, Sec. V will summarize the current study and present conclusions.

II. PRESENT USES AND REQUIREMENTS FOR STABLE ISOTOPES

A. *Nuclear Physics*

Nuclear physics involves the study of the structure and properties of nuclei, and is aimed at an understanding of the basic force which holds the nucleus together. The nucleus is perhaps the most versatile quantal many-body system available in nature. It exhibits a wide variety of interesting and complex phenomena, ranging from single particle features (shell structure) to collective features (vibrations, rotations).

In the last decade there have been considerable changes in the study of nuclear physics. For example, there has been a shifting emphasis from "light ion" beams ($A \leq 4$) to "heavy ion" beams ($A \geq 6$), and also a trend toward higher beam energies. These trends have opened up new vistas in nuclear physics research which are now being exploited. To give an overview of the needs for separated stable isotopes in this field, Table I lists reported usage in the last three years. Most of the isotopes have been used as target materials, although the use of some isotopes for producing beams has been reported. It is expected, however, that the use of isotopically enriched beam materials will increase significantly as the new generation of accelerators comes on the air. [It should be noted here that present machines often use gaseous isotopes, e.g., ^{2}H, ^{3}He, ^{18}O, ^{86}Kr, and ^{136}Xe, as beams, but these have been omitted from the present survey because they are not electromagnetically separated.]

In the view of this author, the distinction between nuclear chemistry (as opposed to radiochemistry) and nuclear physics is somewhat arbitrary. Physicists, for example, have been known to study the fusion and deeply inelastic scattering processes, and chemists have been known to do DWBA

calculations. For this reason, the examples described below, which typify the uses of stable isotopes in nuclear physics, include topics from what is sometimes designated as nuclear chemistry. The area of radiochemistry is covered separately in Sec. II-C.

Light Ion Physics

High Resolution Work

Light ion beams, such as protons or deuterons, can be used to measure single-particle properties of nuclei. Because experiments using these beams can be done with very high resolution, a great deal can be learned about the fine details of nuclear level structures. For example, (p,p) resonance experiments have been carried out at the Triangle Universities Nuclear Laboratory with an overall energy resolution of about 400 eV.[1] Such experiments allow observation of various size resonances and determination of proton strength functions. This type of work necessitates the use of very thin and uniform targets. For the work described in Ref. 1, targets of 2 $\mu g/cm^2$ (on a carbon backing) were employed.

Polarized Beams

Reactions of light ions can also be studied with polarized beams of protons or deuterons. In this case the measurements give information about various single-particle or collective states,[2] that is, ℓ-values, spins and parities, spectroscopic factors, etc. Particularly in the case of spin determinations, the addition of analyzing power measurements can greatly enhance the sensitivity of the experiment. By making comparisons with theoretical nuclear structure calculations across a range of isotopes, it is possible to understand many details of the nuclear structure, such as the influence of deformation or pairing on level schemes, and whether a particular nucleus is better described as vibrational or rotational. For example, a coupled-channels analysis of polarized deuteron inelastic scattering data on the Ge isotopes (Ref. 2) lends support to theoretical predictions[3] of a change in shape from oblate to prolate in going from ^{72}Ge to ^{74}Ge. Targets for this type of work are usually thicker than those required for

ultra-high resolution work. Typical thickness values would be in the 0.1-1.0 mg/cm^2 range. Given the losses in the target preparation process, the amount of isotopically separated material required would be about 5-50 mg per target foil.

Giant Resonances

The study of giant resonance phenomena gives interesting information on the collective structure of nuclei. Besides the familiar giant dipole resonance, evidence has been found in recent years for both giant quadrupole resonances (GQR) and giant monopole resonances (GMR) via inelastic scattering of protons and alpha particles.[4,5] Observation of the GMR allows a determination of the compression modulus of nuclear matter (which depends, in turn, on the nuclear force) if one measures the position of the resonance over a large mass range. In addition, the influence of deformation has been elucidated by comparing data from ^{144}Sm and ^{154}Sm.[5] The GMR apparently splits into two components in the deformed nucleus (^{154}Sm), one component being degenerate with the nearby GQR. One puzzling feature of the present data is the apparent absence of the GMR in lighter nuclei, $A \leq 90$. This aspect will be pursued in future work. Because the widths of the giant resonance states are large (several MeV), there is no particular advantage to thin targets. Target thickness values of 2-10 mg/cm^2 are not unusual in these experiments, leading to requirements for enriched materials of as much as 500 mg per target foil.

Exotic Nuclei

An area of light ion induced reactions which depends critically on the availability of separated isotopes is that involving the production of nuclei far from the valley of beta stability. Mass measurements of such exotic nuclei may be used to test predictions of various theoretical models, e.g., that of Garvey-Kelson[7] or the extensive shell model calculations of Cole et al.[8] As might be expected, most models predict the ground state masses of known nuclei reasonably well, but their predictions tend to diverge as one goes farther from stability.[9,10] Experimentally, one finds that the cross sections for reactions leading to exotic nuclei are small, and that reactions

on isotopic target impurities often lead to considerably higher cross sections (and considerably less negative Q-values), potentially eliminating the ability to observe the more interesting rare nuclei. For example, the "uninteresting" reaction $^{64}Ni(\alpha,^{8}He)^{60}Ni$ has a Q-value of -31.8 MeV and a cross section of about 30 nb/sr, while the corresponding values for the $^{58}Ni(\alpha,^{8}He)^{54}Ni$ reaction,[12] which leads to an essentially unknown nucleus only two neutrons removed from doubly-magic ^{56}Ni, are -50.2 MeV and 0.5 nb/sr, respectively. Existence of a significant ^{64}Ni impurity in the target used by Tribble et al.[12] would have made the measurement impossible.

Work of this type[13-15] also allows the observation and mass measurement of complete isospin multiplets, and provides information on the possible existence of high-order charge-dependent forces in nuclei. Although evidence for such forces has been seen in very light systems (where some members of the multiplet are unbound to particle decay), recently completed measurements of the A=36 isospin quintet indicate[15] no evidence for deviations from the simple quadratic form of the Isobaric Multiplet Mass Equation when all members of the multiplet are bound against isospin-allowed particle decay.

Choice of a target thickness for this category of experiments requires making a compromise between the opposing requirements of good energy resolution (favoring thin targets) and adequate counting rates (favoring thick targets). In practice, the tendency is to favor the latter requirement, since poor resolution data are clearly better than no data at all. Typical targets would have a thickness of 0.2-2.0 mg/cm^2 and would require about 10-100 mg of enriched material for each foil. Even more critical for this work, of course, is the need for highly enriched materials, usually of the low abundance isotopes on the neutron-poor and neutron-rich extremes of the isotope distribution.

Heavy Ion Physics

Deeply Inelastic Scattering

One field of research specific to heavy ions is the study of the deeply inelastic scattering (DIS) process. This process involves the relaxation or

equilibration of a number of degrees of freedom, such as the mass distribution and the kinetic energy. Many researchers worldwide are seeking to determine the mechanism and time scale of the DIS process, and to understand the magnitude and alignment of the angular momentum transferred during the reaction and the nature of the de-alignment that occurs with increasing contact time (increasing kinetic energy loss) between the fragments. Observation of the angular correlation of fragments from the sequential fission of the recoiling target-like nucleus has shown[16] that the angular momentum transfer to the target fragment in DIS of ^{86}Kr + ^{209}Bi or ^{238}U is quite large, J ~ 40 $\hbar$, and that the alignment is also quite high, P_{zz} ~ 0.85. Experiments on similar systems which include detection of emitted neutrons have shown[17-19] that the kinetic energy damping and the neutron-proton ratio equilibrate very rapidly, in about (5-10)x10^{-22} sec.

Targets for these experiments are generally about 0.1-0.5 mg/cm^2 and require about 5-25 mg of material for each foil. For experiments where only light particles are of interest, thicker targets (1-2 mg/cm^2) are usable, provided they can survive the heating due to the beam without melting.

Anomalous Large Angle Scattering

One of the more interesting phenomena discovered in recent years is the so-called Anomalous Large Angle Scattering (ALAS) seen in certain heavy ion systems. Although qualitatively similar behavior had been observed in the scattering of very light heavy ion systems, e.g., ^{16}O + ^{12}C,[20] in which exchange effects might be expected to play a role, its appearance in heavier systems, such as ^{16}O + ^{28}Si (Ref. 21) and ^{12}C + ^{28}Si (Ref. 22), was unexpected. The ALAS phenomenon, which also manifests itself in excitation functions,[22,23] seems to fall outside the standard optical model description of elastic scattering.[24] Structure effects are clearly important here, since the addition of a single nucleon to the lighter fragment, i.e., ^{13}C + ^{28}Si, is enough to completely damp out the oscillations.[22] On the other hand, adding one or two nucleons to the heavier fragment, e.g., ^{16}O + ^{29}Si or ^{16}O + ^{30}Si, reduces the cross sections by a factor of about 5, but does not eliminate the structure.[25] The most recent results[25] suggest that the structure begins to disappear beyond about $E_{c.m.}$ = 45 MeV, but this cannot

be concluded firmly without higher energy data. Although various attempts have been made to explain the existing data, it cannot as yet be said to be fully understood.

In this type of experiment, much of the "back angle" data are actually measured with reverse kinematics at forward angles, i.e., a beam of ^{28}Si on a target of Al_2O_3. Because of the requirement for rather good energy resolution, targets are usually fairly thin, about 0.1 mg/cm^2. Thus, only 5 mg of enriched material might be needed for each target. On the other hand, a separated isotope beam might require several grams of material.

Fusion

There have been extensive studies of the energy dependence of the fusion process in the lighter heavy ion systems. In certain systems composed of "alpha-particle" nuclei, such as $^{16}O + ^{12}C$, unexpected oscillations have been observed[26] in the fusion cross sections in the energy region where they begin to deviate markedly from the reaction cross section. Other nearby systems, such as $^{18}O + ^{12}C$ and $^{19}F + ^{12}C$, however, do not show such behavior[27] and seem to have a very smooth energy dependence to the fusion cross sections. It is now known[28] for $^{16}O + ^{12}C$ that most (>80%) of the fusion cross section goes into just three products, ^{20}Ne, ^{23}Na, and ^{24}Mg, and that the oscillations appear in all channels, but mainly in the ^{20}Ne channel. Also, measurements using gamma-ray detection techniques indicate[29] that, in contrast to Ref. 27, the $^{18}O + ^{12}C$ system does show oscillations, albeit considerably weaker ones than those seen in the $^{16}O + ^{12}C$ system. Evidence on whether the structures observed in the fusion cross sections correlate with those seen in elastic scattering is presently contradictory.[26,28] It does seem clear, however, that a full understanding of the phenomenon will require careful studies in nearby systems.

In determining fusion cross sections directly by detecting evaporation residues, the energies of the outgoing fragments are not very high, and the cross sections are reasonably large. Moreover, the search for structure in the fusion excitation functions requires that the thickness of the target (in terms of energy loss and straggling) be small compared with that of the structure being investigated. These aspects dictate very thin targets

(<0.1 mg/cm^2) for the type of measurements reported in Refs. 26-29, with a corresponding requirement of less than 5 mg of material for each target. In heavier systems, on the other hand, there appears to be no structure, and the laboratory energies of the recoiling fragments are reasonably high. Thus, in these cases somewhat thicker targets, say 0.5-1.0 mg/cm^2, are often acceptable; this means that 25-50 mg of enriched material are needed for each target foil.

Another area of research related to the study of the fusion process involves the question of "complete" versus "incomplete" fusion. At high bombarding energies, Zolnowski et al.[30] have observed a considerable number of forward-angle, high-velocity alpha particles which are in coincidence with fusion-like processes. Even in very heavy systems there are observations[31,32] of considerable emission of forward-peaked protons and alphas which appear in coincidence with fission fragments. The observation in heavy systems of ℓ_{crit} values for fusion which substantially exceed the ℓ value for which the liquid drop model predicts the fission barrier to vanish may be related to angular momentum removal by these fast particles. It has been demonstrated in at least one case[33] that the fast alpha particles emitted during incomplete fusion reactions do tend to come selectively from the higher partial waves. In any case, if the suggestion[31] that these particles are emitted very early in the reaction process turns out to be correct, they will provide an important probe of this interesting stage of the interaction between two heavy ions.

The study of incomplete fusion described in Ref. 30 is carried out by measuring alpha particles in coincidence with gamma rays. For these measurements the target thickness is generally not a limitation, and thickness values in the range of 0.5-5.0 mg/cm^2 have been utilized. This corresponds to about 25-250 mg per target.

High Spin States

One of the special features of heavy ion projectiles is their ability to impart considerable angular momentum to a nucleus, via either (HI,xn) reactions or Coulomb excitation. In several rare earth nuclei, (HI,xnγ) reactions have shown that there is an anomalous increase in the moment of

inertia that occurs at about the I=12 level; this phenomenon is called "backbending." It is explained in terms of the crossing of the ground state band by another even-parity band with a higher moment of inertia. This idea has been nicely demonstrated recently for the nucleus ^{164}Er by Kistner et al.[34] and by Yates et al.[35] Using both (HI,xn) and Coulomb excitation techniques, Yates et al. were able to follow the ground band sequence to $I=22^+$ and also to locate an even-spin "superband" with a large moment of inertia which crosses the ground band at $I=12^+$ as well as two other bands (one positive and one negative parity) which also have large moments of inertia. Experiments of this type provide very detailed tests of nuclear structure models such as the rotation alignment model[36] or the Coriolis anti-pairing model.[37]

Another feature of heavy ion reactions important for nuclear structure studies is their ability to impart considerable linear momentum (recoil velocity) to the final system. To take advantage of this aspect, Andrews et al.[38] have studied continuum states in rare earth nuclei by means of Coulomb excitation experiments with ^{86}Kr. If the products recoil out of the target into a polarized ferromagnetic medium, they experience a very large transient magnetic field (~ 4000 T) which allows determination of g-factors of states having sub-picosecond lifetimes. In studying the Coulomb excitation of ^{160}Dy and $^{170,174}Yb$, for example, Andrews et al. showed that the g-factors decreased at higher spin values, suggesting a weakening of neutron pairing relative to proton pairing.

All of the experiments discussed in this subsection involved detection of gamma rays. For this reason, the targets can be reasonably thick. A typical target thickness for a Coulomb excitation experiment would be about 1 mg/cm^2 (requiring about 50 mg of enriched material), while for the (HI,xn) experiments targets of 5-50 mg/cm^2 have been employed (requiring 250-2500 mg of material per target).

Exotic Nuclei Revisited

The availability of heavy ion projectiles has considerably enhanced our ability to produce and study nuclei far from stability, and thus provides an opportunity to observe nuclei under very unusual conditions. Because of the

wide variety of products which can be formed in a given reaction, such studies frequently employ on-line isotope separators, such as UNISOR,[39] Tristan,[40] RAMA,[41] etc. A typical target thickness here would be 1-3 mg/cm^2, corresponding to about 50-150 mg of material. (A recent survey of developments in this field can be found in the proceedings cited in Ref. 39.) Many interesting nuclear properties can be observed in this fashion, e.g., coexistence between spherical and deformed shapes,[42] existence of triaxial shapes,[43] etc. These properties are best elucidated[44] by following the systematic trends of particular levels across a series of isotopes, e.g., $^{187\text{-}201}$Tl. In addition to the normal spectroscopic techniques, it is also possible[45] to use the mass-separated beams to measure hyperfine splittings and isotope shifts, which will yield information on spins and rms charge radii for nuclei heretofore inaccessible. This topic will be discussed in Sec. II-D below.

The deeply inelastic scattering process discussed earlier can also be used as a means to produce exotic nuclei. It has been shown[46] that the yield of projectile-like fragments can be explained in terms of a statistical transfer of particles between the target and projectile while the two are in contact, followed by a statistical evaporation of light particles from the highly excited primary projectile-like nuclei. As a result, several groups have demonstrated[46,47] that choosing a neutron-rich target can lead to production of exotic nuclei, such as ^{41}Cl, ^{53}Sc, and ^{55}Ti, with cross sections of 0.1 to 1.0 mb. A target thickness of about 0.5-1.0 mg/cm^2 (requiring 25-50 mg of material) is typical for this type of experimental work.

Another worthwhile technique for the study of exotic nuclei employs the fragmentation of relativistic heavy ion projectiles. Westfall et al.[48] produced 14 new nuclides, ^{22}N, ^{26}F, ^{33,34}Mg, ^{36,37}Al, ^{38,39}Si, ^{41,42}P, ^{43,44}S, and ^{44,45}Cl, by looking at projectile fragments at 0^o arising from interactions of ^{48}Ca + ^{9}Be at a calcium beam energy of 212 MeV/A. Given the availability of suitably enriched isotopes, there is no reason to believe this technique would not work equally well with a beam of, say, ^{96}Zr or ^{100}Mo. The thickness of the ^{9}Be target (900 mg/cm^2) was of secondary importance in this experiment, since the beam was the actual source of the interesting reaction products. The amount of source material required for a

^{48}Ca beam is about 0.5 g of enriched material for each electrode (3 are available). Fortunately, it is possible to recover roughly 80% of the unused material from the ion source parts. For the experiment described in Ref. 48, the estimated use rate of ^{48}Ca was about 10 mg/day prior to recovery, or a net usage of about 2 mg/day.

Neutron Physics

Radiative Capture

The study of nuclear structure with slow neutrons is one of the oldest branches of nuclear physics. Many early experiments were accomplished with neutrons from Ra-Be sources, but modern work takes advantage of the high neutron fluxes available at research reactors, such as the High Flux Beam Reactor at Brookhaven National Laboratory. A major use of reactor neutrons is for radiative capture, i.e., the study of (n,γ) reactions[49,50] using thermal or epithermal neutrons. Compared with most other types of nuclear physics experiments, targets for radiative capture can be quite thick: 5-10 g of enriched material are often required. [Fortunately, however, these samples are used with low beam intensities which do not cause significant activation. Thus, the required isotopes can sometimes be borrowed from the Loan Pool at ORNL.]

One virtue of radiative capture (in contrast to charged-particle) work is its non-selectivity[51] -- essentially all nuclear levels with spins close to that of the capturing state are populated. Thus, radiative capture reactions allow sensitive tests of various nuclear models by making it possible to observe many of the rotational bands in nuclei[52] (and sometimes the transitions between them) as well as such quantities as E1 and M1 photon strength functions in a wide range of nuclei.[49,53] Experiments can be done with very high precision by detecting the emitted gamma rays with a curved crystal spectrometer rather than a Ge(Li) counter. Also, knowledge of transition multipolarities can be greatly extended by measurements of conversion electrons with a suitable spectrometer.[53] In high precision gamma ray work it is necessary to use much smaller samples, i.e., several milligrams rather than several grams, in order to prepare small, intense sources for the

spectrometer. These experiments are usually carried out with an in-pile target in order to maintain acceptable rates.

An example of the structure information which can be obtained via radiative capture is given in Ref. 51. In this experiment, levels of ^{109}Pd were investigated to locate the $g_{7/2}$ and $h_{11/2}$ neutron strength. Earlier (d,p) experiments[54] had indicated that, contrary to shell model expectations, the $g_{7/2}$ orbital in ^{109}Pd was nearly empty, while the normally higher lying $h_{11/2}$ orbital was nearly full. Casten et al.[51] have resolved this question by demonstrating that many of the $7/2^+$ assignments in the earlier work were incorrect. After making appropriate modifications to the previously reported spectroscopic factors, the apparent discrepancy was eliminated.

Besides the uses of separated stable isotopes for target materials, several particular isotopes are used for other special purposes. One example is the use of ^{6}Li and ^{10}B as neutron attenuators; this requires several kilograms of each isotope. Another example is the use of ^{45}Sc and ^{56}Fe as neutron energy filters. Because of destructive interference between the s-wave resonance and potential scattering amplitudes, each of these isotopes has a particular energy region (1.95 ± 0.5 keV and 24.3 ± 1 keV for Sc and Fe, respectively) where the total neutron cross section has a sharp minimum. In this region a more or less monoenergetic flux of neutrons is transmitted. About 10 kg of ^{56}Fe were needed to build the neutron filter at BNL. The year the material was obtained from ORNL it put the basic research community back into the big leagues of isotope usage - but only temporarily!

Neutron Scattering and Total Cross Sections

Nuclear deformations can be observed by looking at either the charge distribution or the matter distribution. (In principle, these need not be the same.) Neutrons can serve as an effective probe of the matter deformation of nuclei (as opposed to the charge deformation, which can be studied via electron scattering) by measurements of elastic and inelastic scattering and also total cross sections. Shamu et al.[55] have made a detailed study of deformation effects in various pairs of rare earth nuclides, such as $^{148,154}Sm$, over the energy range from about 1-14 MeV. (In each case about 40 g of isotopically enriched material was used as a target.) They found

rather marked effects (as much as 10%), which are quite accurately reproduced with coupled-channels calculations where the influence of the first 2^+ state is explicitly included. The calculations also shed light on the question of whether a rotational or vibrational coupling scheme gives the more appropriate description of the nuclei studied. Thus, it has been nicely demonstrated that neutron total cross section and scattering measurements offer a very precise means of studying deformations of the matter distributions of nuclei.

Electromagnetic Interactions

Electroexcitation

Electron scattering can be utilized to gain a better understanding of various aspects of nuclear sizes and nuclear structure. One example is the search for giant multipole states. We have already discussed the ability of light ion inelastic scattering to locate such states, but inelastic electron scattering can also be used for this purpose. With light targets, electron scattering experiments are quite sensitive to the distribution of quadrupole as well as dipole strength. In ^{24}Mg, for example, all of the GQR strength was observed in the (e,e′) reaction[55] at energies from 100-200 MeV, while only about 50% of the strength was found using inelastic alpha-particle scattering. Determining the spreading of the E2 strength will ultimately allow a sensitive test of nuclear structure calculations in this mass region.

Single-particle transitions are also well identified in (e,e′) experiments in light nuclei. Using 70-340 MeV beams from the Bates Linear Accelerator, Hicks et al.[56] studied the $^{27}Al(e,e')$ reaction and were able to distinguish the character of the "particle" states (configurations based on excitation of an sd-shell particle into the fp-shell) from the "hole" states (configurations based on a 1p-shell hole in a ^{28}Si core) via the different form factors for the electroexcitation. Comparisons with both strong- and weak-coupling models indicate that neither is entirely satisfactory in explaining the spectrum of the negative-parity levels in ^{27}Al. Here too, moderately thick targets, 10-50 mg/cm^2, are employed; the corresponding requirement for separated isotopes would thus be about 500-1000 mg per target.

Photonuclear Reactions

Photonuclear reactions allow study of the decay properties of the GDR in heavy nuclei, including photoneutron emission and photofission,[57] because photons are most strongly absorbed into this "state." From the total photoabsorption cross sections, values for the axis ratio of deformed heavy nuclei can be determined or, equivalently, the deformation parameter β_2 or intrinsic quadrupole moment. The values obtained in Ref. 57 by this means agree well with values derived by other techniques. In addition, data on the relative amounts of first- and second-chance fission could be obtained; this separation may aid substantially in our understanding of the details of the fission process. Sample sizes used for these experiments ranged from 20 to nearly 300 g.

In light nuclei, it is possible to observe photoneutron emission from many low-lying states reached via E1, M1, or E2 photoexcitation. Holt et al.[58] have studied this process with a ^{13}C target and determined the ground state radiative widths based on a multilevel, multichannel R-matrix analysis. Surprisingly, the results for the strongly interfering E1 excitations at 7.69 and 8.19 MeV agree well with simple weak-coupling wave function predictions but disagree with more sophisticated shell-model calculations. The targets employed in studies such as this can be quite massive; that used in Ref. 58, for example, was about 40 grams.

Photon Scattering

The measurement of elastically and inelastically scattered photons can also provide valuable information on nuclear properties. Compared with scattering of charged particles, photons have the advantage of interacting with nuclei in a well-known fashion, undisturbed by Coulomb effects. Measurements of photon scattering angular distributions allow a determination of the strength distributions for low-multipole giant resonances (E1, M1, E2).[59] In a recent experiment, Bowles et al.[60] used nearly monochromatic photons to measure both elastic and inelastic photon scattering to the GDR region of ^{52}Cr, ^{60}Ni, and $^{92,96}Mo$, and have compared their results to a model which calculates photon decays of the GDR including coupling to the low-lying quadrupole states. Strengths of the inelastic scattering to the 2^+

levels in these nuclei are at least qualitatively reproduced by the model, but it was found necessary to include an additional isospin splitting of the GDR in the calculations in order to obtain detailed agreement with the data. Here too, targets of several tens of grams can be conveniently employed.

Weak Interactions

Double Beta Decay

Moe and Lowenthal[61] are pursuing an experimental hunt for double beta decay in ^{82}Se. They hope to find direct evidence for this process, either with or without neutrino emission. The choice of ^{82}Se was based on its very favorable decay energy (3 MeV), its chemical stability in elemental form, and existing geochemical evidence for a half-life for double beta decay (~ 10^{20} years) which is within the range of a direct measurement. Using 38 grams of 97% enriched ^{82}Se, a target was fabricated which can be viewed by a cloud chamber. Based on the observation of 20 double electron events which had an energy and angular distribution consistent with the process of double beta decay with neutrinos (and which did not appear to be caused by background events), Moe and Lowenthal feel they have obtained suggestive, but not conclusive, evidence for this process. The tentative half-life based on the present observations is about 1×10^{19} years. Improved experiments are under way to obtain more definitive results.

B. Medium Energy Physics

Medium energy physics is an extension of lower energy nuclear physics into a regime where meson production becomes significant. One of the important topics being studied is that of the matter distributions in nuclei. (High energy electron scattering does a good job of providing information on the proton distributions in nuclei but provides relatively little sensitivity to the neutron, or matter, distributions.) A strongly interacting probe seems to be most suitable for investigating the neutron distribution in nuclei. In fact, it appears that pions may be an excellent choice for this task. The reason is that, in the energy region near the (3,3) resonance, the scattering of

negative pions is much more sensitive to neutrons than to protons -- a unique feature among strongly interacting probes. Hopefully, the interaction of pions with nuclei will ultimately provide information not only on nuclear sizes but also on the equation of state of nuclear matter, pion condensation, etc.

At existing medium energy accelerators, e.g., the Los Alamos Meson Physics Facility (LAMPF), the fluxes of π^+ and π^- beams are still rather modest ($\sim 10^8$/sec and $\sim 10^7$/sec, respectively) compared with typical nuclear beams, and the beam spot sizes can be fairly large. For these reasons, the amount of target material required for a medium energy physics experiment is generally considerably larger than that required for most nuclear physics work. Typical target thicknesses for the experiments described in this section are in the range of 100-1000 mg/cm^2, compared with a value of more like 1 mg/cm^2 in the majority of the work described in Sec. II-A. The use of separated isotope materials in medium energy physics for the past three years is shown in Table II. Although the variety of isotopic species is presently much less than for nuclear physics (cf. Table I), the amount per sample is usually in the range of 10-100 grams. Note also that for those elements which are presently required, there is generally a need for a wide range of isotopes. This has to do with the fact that, at the present stage of development, it is often prudent to compare data from several isotopes in order to determine the requisite nuclear structure information in the most model-independent fashion. Several examples of this approach will be discussed below.

Proton Scattering

Neutron Density Determination

Elastic scattering of medium energy protons ($E_p \sim 1000$ MeV) is a powerful technique for investigating the matter distribution of nuclei. Such investigations give important information which may be compared with theoretical nuclear structure determinations of ground state matter densities, such as those from Hartree-Fock calculations. A group at LAMPF, for example, has recently completed a study of the p + ^{208}Pb system at

E_p = 800 MeV.[62] They analyzed their data in terms of a spin-dependent optical potential formalism which uses on-shell proton-nucleon scattering amplitudes as its basic input and treats the target protons and neutrons independently. Hoffmann et al.[62] used a three-parameter Gaussian form for the neutron density in ^{208}Pb and took the proton density from existing electron scattering data, as described in Ref. 63. A careful error analysis, including both experimental errors and uncertainties related to the choice of nucleon-nucleon scattering amplitudes, indicated that the neutron density is determined very well from about 3.5 to 9.0 fm, and that the rms neutron radius in ^{208}Pb is 5.593 fm, or 0.14 $\pm$ 0.04 fm larger than the corresponding proton radius.

A similar analysis was carried out in Ref. 64 for the Ca isotopes. In that case, it was found that the absolute values for the neutron radii in the various isotopes depend markedly (~ 0.2 fm) on the input scattering amplitudes chosen. On the other hand, the relative differences in the neutron radii between isotopes were essentially independent of the choice of scattering amplitudes and were therefore greatly superior in terms of a meaningful comparison with theory. A study by Ray et al.[64] indicated that Hartree-Fock calculations do a good job of predicting the relative neutron radius changes with respect to ^{40}Ca for all the isotopes except ^{48}Ca, whose neutron skin is not as thick as had been predicted. Targets used for these experiments ranged in thickness from 20 mg/cm^2 at forward angles to 150 mg/cm^2 at backward angles.

Pion Induced Reactions

Pure Proton and Neutron Transitions in Nuclei

In pion scattering from free nucleons near the (3,3) resonance, the ratio of π^- to π^+ cross sections is about 1/9 for protons and 9 for neutrons. In studies of π^- and π^+ scattering leading to collective states in even-even nuclei, however, the observed ratios are close to unity, presumably reflecting the more or less equal contributions of proton and neutron excitations. In contrast to these results, two recent studies of π^+ and π^- inelastic scattering from ^{13}C at 162 MeV[65] and 180 MeV[66] have located a state at 9.5 MeV

with a strong enhancement in π^- scattering and another state at about 16 MeV with strong π^+ enhancement. Compared with free-nucleon values, the enhancement of the 9.5 MeV state is essentially consistent with a pure neutron excitation, while the state at 16 MeV is consistent with a pure proton excitation. Several lower-lying states which are thought to be mainly single-neutron configurations do not show much enhancement, which suggests that they may be significantly admixed with proton particle-hole components. These data are an encouraging sign that pion scattering will become an increasingly important tool in the study of nuclear structure.

This comparison technique was recently extended[67] to pion scattering from a ^{14}C target, with even more striking results. In this case, enhancement factors even larger than the free-nucleon estimate of 9 were found for several states. Preliminary analysis indicates that this can be explained in terms of destructive interference between the proton and neutron components of certain 2-hole and 2-particle-4-hole configurations in the wave functions.

As mentioned earlier, the low beam intensities available for these experiments dictate thick targets. For the work described in Ref. 65 the 99% enriched ^{13}C target had 72.5 g of material, while 9 g of ^{14}C was used for the experiment described in Ref. 67.

Pion Charge Exchange

Analog states in nuclei, where all quantum numbers are the same except for the isospin, have been known and studied for many years.[68] Recently, Baer et al.[69] have investigated the (π^+, π^0) reaction on a variety of targets, ranging from ^7Li to ^{208}Pb, at a pion energy of 98 MeV. In each case a very strong peak was observed in the π^0 spectrum at precisely the energy expected for the analog state. Calculations are under way to use such states to obtain more information on the isospin-dependence of various higher-order terms of the pion-nucleus interaction responsible for their production. Because of the low π^0 production rate, exceedingly thick targets, ranging from 500-1200 mg/cm^2, were used for this experiment.

Several other groups[70,71] have been studying the pion double charge exchange (DCX) reaction (π^+, π^-). This process can probe high isospin

states and can be used to produce exotic nuclei. In a simple picture, it would be expected that this reaction would populate mainly the analog state in the final nucleus. However, the data of Seth et al.[70] for the reaction $^{18}O(\pi^+,\pi^-)^{18}Ne$ show that the non-analog $^{18}Ne(2^+)$ state is populated with the same intensity as the analog transition to the ground state. In addition, they found that they could not fit their angular distribution for the ^{18}Ne(g.s.) with any of the existing reaction theories for the DCX process. Fortunately, the same process, when studied[71] at a higher beam energy of 292 MeV, does appear to exhibit the expected selectivity. Thus, it appears that the DCX reaction will be extremely useful for locating "T+2" analog states in nuclei. For these difficult experiments, targets as thick as 900 mg/cm^2 have been employed.

X-Ray Studies

Nuclear Charge Distributions

It is by now well known that x-ray measurements of muonic atoms can provide very sensitive information on the nuclear charge distribution, including in some cases both static and dynamic quadrupole moments. Powers et al.[72] have studied muonic x-rays (transition energies and hyperfine splittings) in the whole series of isotopes $^{144,147,148,149,150,152,154}Sm$ and analyzed their data in terms of a deformed Fermi distribution for the charge density of each isotope. They found that such an analysis must take into account the possibility that the nucleus will be excited during the course of the muon cascade; due to its large deformation, the probability that ^{154}Sm will be raised to its 2^+ first-excited state is nearly 40%. This excitation shifts the position of the 1s atomic level by more than 1 keV. In terms of equivalent charge radii, Powers et al.[72] found that the change from ^{144}Sm to ^{154}Sm is 0.19 fm, a result which agrees well with other methods of determining this quantity.

Pion-Nucleus Potential

Although the bound atomic pion is not especially useful as a probe of nuclear charge distributions (due to the fact that it interacts via the strong force as well as the well-understood electromagnetic interaction), it offers the possibility of determining some of the properties of the pion-nucleus interaction potential. This can be done by choosing "reference" nuclei for which the charge distribution is already well known from electron scattering and/or muonic atom results, and for which the neutron density is calculable from a good model, such as Hartree-Fock. Powers et al.[73] have used the isotopes of even-even nuclei with $6 \leq Z \leq 16$ for this purpose. A phenomenological potential was obtained from these data by fitting the x-ray results using the Klein-Gordon equation along with a complex optical potential of the type suggested by Ericson and Ericson.[74] Experiments were performed on a series of "test" nuclei, $^{40,42,43,44,48}Ca$ and $^{46,48,50}Ti$, to see if the empirical potential parameters derived from the reference nuclei would lead to a correct determination of neutron distributions in the test cases. Since the stopped pion rate was very low, $5 \times 10^{-6}/(g/cm^2)$-sec, target materials ranged from 2.5 to 14.7 g samples. Data were obtained with a Ge(Li) detector for both transition energies and widths for the 3d to 2p transitions in the Ca and Ti isotopes. At least for these cases, the empirical potential leads to reasonably good agreement for the neutron radius shifts compared with determinations by other techniques (e.g., Ref. 64). If the potential parameters can be fixed in other mass regions, the technique of using pionic atoms for information on the neutron distribution can be extended.

C. Radiochemistry

The question of what topics qualify as "radiochemistry" in the context of stable isotope usage is somewhat fuzzy, since techniques involving radiochemical methods have found wide applicability in many areas of research. Radiochemistry will be used here to mean those areas of nuclear chemistry which utilize chemical techniques for at least a part of their research effort. The topics to be covered here include transactinide

chemistry, fission studies, high energy spallation reactions, and the search for superheavy elements. Nuclear or radiochemical techniques used in the study of other types of physical and chemical problems (e.g., Mössbauer spectroscopy and perturbed angular correlations) will be covered in Secs. II-D and II-E.

Table III shows the use of stable isotopes in radiochemistry over the last three years. Compared with Tables I and II, the distribution of isotopes in Table III tends to be somewhat more concentrated in the high mass half of the periodic table.

Heavy and Superheavy Elements

Transactinide Chemistry

One important area of radiochemical work involves the study of the chemical properties of transactinide elements. Such information can be valuable in making a determination of the atomic number of an unknown radioactive species, as well as for establishing the chemical behavior of yet-to-be-discovered heavy elements (see below), where a chemical separation might be a necessary means of identification. In practice, such studies are becoming more difficult both because of short half-lives for many newly discovered heavy nuclides and because of exceedingly small production cross sections.

The chemistry of element 104, for example, has been studied[75] to see if it behaves (as predicted) as a chemical homolog of Group IV-B elements Zr and Hf. The isotope ^{261}[104] was produced in the reaction ^{248}Cm(^{18}O,5n) using a (degraded) beam energy of 98 MeV. Because the half-life of this nuclide is only 65 seconds, a computer-controlled fast chemistry apparatus was employed; this device allowed a repetitive chemistry experiment to be done every three minutes. To ensure that the behavior of element 104 was similar to that of Hf, a ^{181}Hf tracer was used in some of the chemistry runs. In spite of detecting only 6 atoms of ^{261}[104], Hulet et al.[75] were able to demonstrate that its chemical behavior differs markedly from Cm and Fm isotopes, and that it is similar to that of Hf.

Search for Superheavy Elements

In recent years, a considerable amount of effort has gone into the attempt to produce and identify so-called superheavy elements (SHE).[76,77] These are elements with Z~114 which are expected to have enhanced stability against fission due to the presence of closed shells. At present, it appears that the most promising experimental approach is the study of the $^{48}Ca + ^{248}Cm$ reaction. A previous study[76] of this reaction produced no evidence for SHE formation. However, one possible "gap" in the search was the fact that the chemical techniques utilized were not very sensitive to highly volatile products. (Elements 112 and 114 are chemical homologs of Hg and Pb, respectively, and thus are expected to have very low boiling points -- that is, below that of Hg. In addition, relativistic Hartree-Fock calculations suggest that the electronic configurations of these elements will be rather stable, leading to the prediction that they may behave somewhat like noble gases.) Illige et al.[77] repeated the earlier experiment using a 267 MeV ^{48}Ca beam incident on a 24 $\mu g/cm^2$ ^{248}Cm target. In this experiment, all non-volatile products were eliminated from the detection system, and any volatile products were trapped on a liquid-nitrogen-cooled surface. Unfortunately, no SHE's (in the half-life range from 1 sec to 10^7 sec) were observed in 4 months of counting. Based on updated theoretical predictions[78] regarding the dynamics of the fusion mechanism, however, there is a possibility that the bombarding energy chosen was unnecessarily high. Therefore, new experiments will be conducted at a lower beam energy, and will use physical as well as chemical techniques to span the widest possible range of half-lives.

The amount of the rare isotope ^{48}Ca used in these experiments is considerably higher than that used for the experiment described in Ref. 48 (see Sec. II-A). Estimated usage here is about 200 mg/day in the ion source; assuming 80% recovery leads to a net usage of 40 mg/day. Should evidence for SHE production be obtained, a further supply of ^{48}Ca would probably be needed. In addition, usage of very heavy target materials would surely increase.

Fission Studies

Fission decay of heavy nuclei is a process which is being extensively studied in a variety of different reactions induced, for example, by thermal neutrons,[79] fast neutrons,[80,81] light ions,[82] heavy ions,[83,84] pions,[85] and even anti-protons.[85] Radiochemical techniques have frequently been employed in such studies,[80,84] since they can provide both Z and A resolution not generally available in experiments where the fission fragments are detected directly. Because the objective of such studies is to determine the fission properties of one particular nuclide, highly enriched targets are very important.[79,80,82]

Several research groups have focused on the determination of mass yields of fission products, primarily via gamma-ray and sometimes via beta-particle spectroscopy. Besides providing data aimed toward a theoretical understanding of the fission process, accurately known fission yields can provide information on fuel burn-up in a nuclear reactor.[86] [It may be necessary, however, to have more precise information for this application than can generally be obtained radiochemically. In this instance, mass spectrometric methods may be utilized. Such studies are generally pursued at industrial laboratories and will not be discussed further here.]

Weber et al.[82] have compared data for ^{252}Cf spontaneous fission to that obtained for fission of ^{252}Cf at excitation energies near the fission barrier produced in the $^{250}Cf(t,pf)$ reaction. They found that the total kinetic energy (TKE) released in the induced fission process is about 5 MeV greater than that from the spontaneous fission. Interestingly, however, the shift toward symmetry in the mass spectrum for induced fission was accompanied by an increase in TKE. This is in contrast to results from other cases in which a symmetric mass split occurs with a somewhat reduced TKE release.

Difilippo et al.[81] studied data on neutron-induced fission with very high resolution. An attempt was made to explain the observed strong resonances at 720 and 1210 eV in terms of population of Class I levels (in the inner well of a double-humped fission barrier) or Class II levels (in the outer well), but their data do not allow an unambiguous choice.

Husain and Katcoff[85] have measured the fission cross sections for Au, Bi, and U targets induced by 1730 MeV anti-protons and 2360 MeV negative pions. They observed that the fission cross section for pions was essentially the same as that for comparable energy protons, but the fission cross section induced by anti-protons was nearly double that for protons. This may be related to the very high excitation energy obtained when the anti-proton annihilates in a nucleus.

High Energy Reactions

Study of the distribution of nuclides produced in high energy nuclear reactions induced by light and heavy ions can provide interesting information on the reaction mechanism. In most cases the range of products is rather broad, and is therefore well-suited to the global nature of radiochemical techniques. (Such studies are also pertinent to other fields of research, such as cosmic ray investigations, cosmochemistry, etc.) One example of this type of work can be found in Ref. 87, in which measurements were reported of the spallation products arising from interactions of 720 MeV alpha particles with targets of $^{92,96,100}Mo$. The data demonstrated that, in spite of previous predictions to the contrary, the yields of spallation products do "remember" the N/Z ratio of the target nucleus. Analysis of the isobaric yields for A=72 showed that the distribution was shifted toward a higher N/Z ratio for the more neutron-rich target, and also that the distribution from this target was skewed toward the high N/Z side. In fact, the most probable N/Z ratio appears to depend linearly on the combined N/Z ratio of the target + projectile system. Several empirical predictions for the isobar yields are able to reproduce the peak shift of the distribution but are presently unable to predict the skewing of the yield curves for different targets.

With the advent of relativistic heavy ion accelerators, experiments can now be performed with a variety of projectiles. Loveland *et al.*[88] have applied thick catcher foil techniques to the study of products from the reactions of 8000 MeV ^{20}Ne + ^{181}Ta at the Bevalac. They found that the condition of "limiting fragmentation" (where the product yields become

independent of the bombarding energy) has apparently not been reached for this system. In addition, they found that products from the Ne + Ta reaction are more forward-peaked than those from proton or ^{12}C bombardments of similar mass targets. Thus, it appears that relativistic heavy ion collisions behave differently than do those of lighter projectiles and that they provide a unique opportunity to gain significant new information on the reaction mechanisms in high energy collisions.

D. Other Chemistry

Aside from the specifically "nuclear" aspects of chemical research, there are several other areas of chemistry which depend critically on the availability of enriched stable isotopes. By far the dominant use is for nuclear magnetic resonance (NMR) spectroscopy. Separated isotopes used in this area include ^{2}H, ^{13}C, ^{15}N, and ^{17}O; all of these, but especially ^{2}H, are utilized in quantities ranging up to hundreds - or even thousands - of grams per year by individual research groups. Another area of chemistry where separated isotopes are routinely used is molecular spectroscopy; substitution of ^{18}O (as well as most of the aforementioned isotopes) into a molecule, for example, will change the rotational or vibrational frequency and thereby make it possible to verify band assignments in such work.[89] An analogous technique is sometimes utilized in mass spectrometric measurements of various molecular reaction products, which can be tagged via isotopic substitution.[90] Finally, isotope effects on various chemical properties, such as vapor pressure, have been investigated.[91] [The technique of Mössbauer spectroscopy, which is important to both physics and chemistry research, will be discussed in Sec. II-E.] Because most of the uses of stable isotopes in chemistry involve the relatively light elements (H, C, N, O) or gases, they will not be covered here. There are, however, growing numbers of chemistry experiments which do utilize electromagnetically separated isotopes. A few examples of such uses appear below. As can be seen from Table IV, the amounts involved are comparatively small, but probably will grow with time.

NMR Spectroscopy

As just mentioned, the commonly used isotopes for NMR spectroscopy include mainly those of the lighter elements H, C, N, and O. However, there are many heavier nuclei with nuclear spin I=1/2 which are useful for this purpose. Acerete et al.[92] have demonstrated the utility of ^{183}W for studying the structure of heteropoly- and isopoly-tungstates via NMR. Although ^{183}W is the only NMR-active tungsten isotope, its NMR sensitivity relative to the proton is 7×10^{-5}; thus, enriching the ^{183}W concentration beyond its natural 14.3% abundance will be important. NMR behavior for ^{25}Mg and ^{43}Ca is reviewed in Ref. 93, while ^{45}Sc, ^{89}Y, ^{139}La, $^{47,49}Ti$, ^{51}V, ^{93}Nb, ^{181}Ta, ^{53}Cr, $^{95,97}Mo$, ^{55}Mn, ^{99}Tc, $^{185,187}Re$, ^{57}Fe, $^{187,189}Os$, ^{59}Co, ^{103}Rh, ^{195}Pt, $^{63,65}Cu$, $^{107,109}Ag$, ^{67}Zn, $^{111,113}Cd$, and last but not least, $^{199,201}Hg$ are reviewed in Ref. 94. In general, the amounts of material required are not excessive; a given researcher would probably need quantities on the order of 0.5-1 g per year.

ESR Spectroscopy

Another area where a wide range of isotopes can be utilized to good advantage is in the study of molecules via the technique of Electron Spin Resonance (ESR). Weltner and collaborators[95-97] have made several studies of the ESR spectra of inorganic molecules trapped in various solids, such as Ar or Kr at 4^{o} K. In each case, an elucidation of the complicated ESR spectrum was accomplished through additional measurements of separated isotope versions of the same compound, e.g., SiN_2 was also observed as $^{29}Si^{15}N_2$, etc. From the ESR spectra it was determined that SiN_2 molecules in a pure N_2 matrix were bent, while the same molecules trapped in Ne were linear. The inference is that the molecular bending force is quite low, and that the constraints in the matrix sites are enough to induce bending of the molecule. As part of the studies reported in Refs. 95 and 96, optical spectra were also unraveled via isotope substitution techniques.

Inelastic Scattering

Dagdigian et al.[98] have studied rotational inelastic scattering of ^{7}LiH molecules in collisions with HCl, DCl, and HCN molecules via a new technique which employs electric quadrupole state selection and laser fluorescence detection. Cross sections leading to various excited rotational states of ^{7}LiH were observed. It was found that the distribution of states is rather narrow and that the cross sections are large, reflecting the long-range coupling between the very polar molecules, such as ^{7}LiH, HCN, etc. Theoretical calculations show that the Born Approximation considerably overpredicts the experimental cross sections, but calculations using a Sudden Approximation agree reasonably well with the data.

Mass Spectrometry

Mass spectrometric techniques utilizing stable isotopes are widespread in chemical research. These techniques are used in the study of molecular reaction mechanisms[99] and also in analytical work to measure concentrations of various species, both stable and radioactive.[100] Many analytical applications are handled with the technique of Isotope Dilution Mass Spectrometry (IDMS), which is described in a review article by de Bièvre.[100] [It was through the use of IDMS on samples of ^{235}U that the discovery was made of a naturally-occurring nuclear reactor which existed at Oklo (Gabon) about 2 billion years ago. This reactor functioned for at least 100,000 years and used up perhaps 1000 kg of ^{235}U.[100]] Because of the accuracy of IDMS techniques, the method can be utilized for half-life determinations if the half-life is in the range of tens of years or if the half-life is very long.[101]

Of particular interest to chemistry is the ability of IDMS to provide very accurate atomic weights for the elements. All recent changes in the atomic weights adopted by the International Union of Pure and Applied Chemistry have come from isotope dilution mass spectrometry, and it is expected[100] that this will hold true in the future. The National Bureau of Standards (NBS) is currently pursuing measurements of this type. In order to obtain absolute isotope ratios, however, it is crucial to calibrate the mass

spectrometer over a wide range of isotope ratios (for each element studied) by means of very accurately known standard isotopic mixtures.[100] Creation of these standards by the NBS requires gram amounts of very highly enriched isotopes. These isotopes must also be sufficiently pure chemically that they can be used to prepare standard mixtures by gravimetric techniques. Without pure raw materials, NBS would be unable to create new standards (which are distributed worldwide) and would therefore be unable to improve the accuracy of atomic weight determinations. An example of the usefulness of such a measurement program can be found in Ref. 102, in which a new value for the Avogadro constant, accurate to 1 ppm, was deduced from very accurate measurements of the atomic weight of natural Si samples, along with careful density determinations and a precise measurement of the unit-cell volume in silicon. [For those who are curious, the result was $N_A = 6.0220943 \times 10^{23}$ atoms/mole.] The IDMS technique is also an important component of chronology determinations in the geosciences. This will be discussed in Sec. II-F.

E. Other Physics

Besides nuclear and medium energy physics, there are two other branches of physics which rely on stable isotopes: atomic physics and solid state physics. Table V lists the isotope usage in the last 3 years for these research categories.

One major use of isotopes in atomic physics is for the study of the so-called isotope shift in optical spectra. As we will see below, new and powerful techniques based on tunable dye lasers are making a significant impact on our ability to measure these shifts, and hence nuclear properties, in regions far from the valley of beta stability.

In solid state physics, Mössbauer spectroscopy allows a very sensitive look at the properties of metals, insulators, superconducting compounds, etc. Such studies can also be used to elucidate the properties of chemical bonds and the effects of various ligands. Thus, applications of the Mössbauer technique are ubiquitous in nuclear physics, solid state physics, chemistry, metallurgy, geology, and biology. A closely related experimental technique is

that of perturbed angular correlations (PAC). This technique has much in common with Mössbauer spectroscopy,[103] since it can be used to probe some of the same effects. One difference between the two techniques, however, is that PAC studies require considerably smaller quantities of isotopes.

Atomic Physics

Laser Spectroscopy

In atomic physics the major impact of the "isotopic" nature of atomic nuclei is the so-called isotope shift, which involves a shift in the centroid of the hyperfine levels between isotopes of the same element. This shift arises in part from the mass change of the nucleus about which the electron rotates,[104] and in part from the change in the charge distribution of the nucleus across a series of isotopes. Especially in heavy nuclei, the former effect is rather small and, in any case, the interesting information about the nucleus comes from the latter effect. [In order to avoid problems with this isotope effect, the international unit of length was defined in terms of the wavelength of a particular atomic transition in ^{86}Kr, rather than natural Kr.] These effects are also the ones being probed with muonic atoms, discussed in Sec. II-B.

In terms of isotope usage, the dominant atomic physics experiments are those involving laser spectroscopy of hyperfine structure. The present status of such work has been reviewed recently by Redi[105] and by Schuessler.[106] As discussed earlier in this paper, the study of isotope shifts can also be carried out with electronic or muonic x-rays. The main benefit of techniques involving optical spectroscopy is that unstable nuclei are also available for study, whereas the x-ray technique is restricted to stable nuclei. Good advantage is being taken of this by coupling laser spectroscopy techniques with existing on-line mass separators.[107-110] In this manner, isotope shifts have been determined for beta-unstable isotopes of Na,[107] Hg,[108,109] and Cs.[110]

A very nice experiment by Bemis *et al.*[111] at ORNL allowed a measurement of the *isomer* shift in ^{240m}Am, a spontaneous fission isomer with a half-life of only 1 msec. The experiment produced the ^{240m}Am

isomer via the $^{238}U(^{7}Li,5n)$ reaction at 47.5 MeV, thermalized the recoils in helium gas, and then polarized the atoms via the LINUP (Laser Induced NUclear Polarization) technique. Rather than use the light itself to detect the resonance condition, Bemis et al. monitored the rate of fission fragments. At the resonant absorption frequency the beam is optically pumped to the atomic state $F=F_{max}$, $M=+F_{max}$ and the aligned nuclei no longer fission isotropically but fission preferentially along the laser axis. Coincident fission detectors at 90^{o} to this axis were used by Bemis et al. to record the decrease in fission-fragment rate when the laser was tuned to the resonant frequency.

Comparing the experimental shift for ^{240m}Am relative to ^{241}Am with that for ^{243}Am relative to ^{241}Am, Bemis et al. found that the change in $\langle r^2 \rangle$ for ^{240m}Am, 4.6 fm^2, was 26.8 times larger than that for ^{243}Am and corresponds to a deformation parameter of $\beta = 0.64$, or a quadrupole moment of 30 b, compared with a ground state deformation of $\beta = 0.24$. Thus, the identification of the fission isomer as a strongly deformed shape isomer was directly confirmed for the first time.

Solid State Physics

Mössbauer Spectroscopy

Nuclear resonance absorption of gamma rays, referred to as the Mössbauer effect, makes it possible to probe in a very sensitive fashion the environment of an emitting (or absorbing) nucleus. In particular, such measurements give information on the isomer shift, the magnetic hyperfine splitting, and the electric quadrupole splitting.[112] The first of these quantities, the isomer (or chemical) shift, measured in terms of the relative velocity of the source and absorber required to obtain resonance absorption, depends on the size differences between the nuclear ground and excited states and also on factors which modify the electron density within the nucleus. The magnetic hyperfine splitting, which gives rise to multiple resonance peaks due to the removal of the degeneracy between different hyperfine levels (for nuclear spin $I \geq 1/2$), depends on the effective magnetic field acting on the nucleus. This field arises from the motion of the

electrons outside the nucleus as well as any externally applied fields. The electric quadrupole splitting also gives rise to multiple resonance peaks, due to the removal of the degeneracy between different orientations of the nuclear quadrupole moment ($I \geq 1$) with respect to the electric field gradient present at the nucleus. Given knowledge of the nuclear dipole and quadrupole moments, the observed Mössbauer spectrum can be compared with model calculations of the electronic structure of a Mössbauer nucleus in its medium in order to determine such details as oxidation states, position(s) in a crystal lattice, etc.

A great many nuclei can be used as Mössbauer sources; the main requirements are that the nucleus have a gamma-ray transition of reasonably low energy, say less than about 100 keV, and that the half-life of the Mössbauer gamma ray be on the order of 1 nsec. By far the most commonly used source is the 14.4 keV transition in ^{57}Fe, fed from decay of ^{57m}Co (270 d). Other commonly used sources include (but are not limited to) ^{61}Ni, ^{99}Ru, ^{181}Ta, $^{180,182,183,184,186}W$, $^{186,188,189,190}Os$, $^{191,193}Ir$, and ^{195}Pt. It is almost always preferable to make the precursor of the Mössbauer emitting nucleus from isotopically separated material in order to optimize the specific activity of the source and minimize resonance absorption in the source material. (Most of the production of these sources is done commercially and will not be discussed here.) In addition to the source production, it is often necessary to have an enriched quantity of absorber isotope. This is because the doping of the material to be studied can be difficult when using, e.g., the 2% abundance of ^{57}Fe in natural iron. Mass separators are sometimes used to dope the material to be studied.[113] Another method is to fuse the materials of interest together under vacuum. The typical amount of material needed for absorber work is about 0.1 g per researcher per year. Source strengths for, e.g., ^{57m}Co, are in the range of 20-120 mCi (100 mCi is about 12 μg of ^{57m}Co). Thus, although the sources are very important, the actual amounts of radioisotopes needed are rather small.

Applications of Mössbauer spectroscopy are quite widespread. A few examples from the recent literature will illustrate some of the uses. Koizumi and Cathey[114] have used a ^{57m}Co source to study the intermetallic

compound $Fe_{0.5}Co_{0.5}Ti$ and its hydride phases. This compound is interesting because of its ability to absorb a tremendous quantity of hydrogen. It is a good choice for Mössbauer spectroscopy because it already contains the absorber, making it unnecessary to dope the material. By comparing Mössbauer measurements as a function of temperature and hydride content, Koizumi and Cathey were able to demonstrate that there is a phase change in the material as the hydrogen content is increased, and that the two phases coexist. In addition, their analysis suggests that the changes in the Mössbauer spectrum arise from the distortion and expansion of the metal lattice, and that the direct contribution of the H atoms is small.

As another example, Suib et al.[115] have studied the behavior of Eu ions as part of a europium-exchanged zeolite catalyst. Although several studies had already been made on such systems, there still existed several ambiguities, one of which had to to with the possible role of Eu^{4+} in the zeolite. By monitoring the Mössbauer spectrum as a function of time, they were able to show that 95% of the Eu exists as Eu^{3+} and that the addition of water to the zeolite gives only Eu^{3+} and shows no evidence for Eu^{4+}.

Of interest to all ^{57}Fe Mössbauer work, Duff et al.[116] have obtained a new value for the quadrupole moment for ^{57}Fe which is only about half of the currently accepted value. They have calculated the electric field experienced by the ^{57}Fe in $FeCl_2$ and $FeBr_2$ via very sophisticated self-consistent-field Hartree-Fock calculations. Their value, coupled with the observed Mössbauer splitting, indicates Q=0.08 b rather than the 0.15 b value presently accepted. Should this be confirmed, it would necessitate re-evaluation of many current Mössbauer experiments using ^{57}Fe.

Perturbed Angular Correlations

The study of perturbed angular correlations, like that of Mössbauer spectroscopy, offers opportunities to learn about the properties of matter in a wide variety of circumstances. [For a discussion comparing the two methods, see Ref. 117.] This technique can be used to measure g-factors of recoiling states,[38] to probe the structure of crystals,[118] or to elucidate chemical bonding in molecules.[119] The "perturbation" used for this purpose is the interaction between the quadrupole moment (or magnetic moment) of

the emitting nucleus and the internal or external electric field gradient (or magnetic field) which it encounters.

Requirements for practical PAC emitters are that they have two gamma rays in cascade, and that the transitions be fed by a decay having a half-life of at least 1 hour. Examples of suitable nuclei include ^{111}Cd, ^{181}Ta, ^{204m}Pb, ^{181}Re, $^{125,127}I$, $^{154,156}Gd$, ^{113}Sn, etc.[120] In general, the specific activity of the material should be high and competing products minimized; these factors argue for using enriched isotope precursors. As mentioned earlier, the amounts of material required for PAC studies are relatively modest compared with the amounts needed for Mössbauer spectroscopy absorbers. A 100 mCi radioactive source of ^{181}Hf, for example, is only about 6 μg of material.

One example of the use of the PAC technique was the experiment of Senba et al.,[118] who studied the temperature dependence of the hyperfine field H_{hf} of various ions implanted in both the hexagonal close packed (hcp) and face centered cubic (fcc) phases of ferromagnetic Co by means of time differential perturbed angular correlations (TDPAC). The reaction $^{100}Mo(^{16}O,3n)$ at 56 MeV was used to populate the 740 keV isomeric state of ^{113}Sn, which recoiled out of the 0.7 mg/cm^2 enriched ^{100}Mo target into the Co backing material. The beam was pulsed at a 1 MHz rate, and two NaI counters were used to observe delayed gamma rays at 45^o to the beam axis during the beam-off periods. Senba et al. were able observe the exponential decay of the time spectrum modulated by the Larmor precession of the metastable state in the hyperfine field (polarized with a 1.7 kG external field). After correcting for the external field, the value of H_{hf} was measured and found to actually change sign at about 800^o C. Through comparison with existing Mössbauer data, it could be concluded that the behavior of H_{hf} is completely independent of the method of implantation.

As another example, Ball and Kaplan[119] studied the interaction of the ^{181}Hf nucleus with its chemical environment via TDPAC. The technique promises to be an informative one, since chemically generated electric quadrupole interactions often reflect specific aspects of the molecular symmetry and electron distributions in chemical bonds. Using high specific activity $^{181}HfOCl_2$ ($t_{1/2}$=42.5 d) in dilute HCl, measurements were carried

out on several different compounds, HfO_2, $HfO(H_2PO_4)_2 \cdot H_2O$, and HfP_2O_7, via the 133 keV - 482 keV cascade. (Because the recoil energy is very low and the half-life of the first gamma ray is 18 μsec, it was expected that any "hot atom" effects would have subsided prior to the cascade.) The data were compared with predictions of H_{hf} based on simple bonding calculations, with fairly good agreement. Ball and Kaplan concluded that the bond structures of the two phosphorus compounds were very similar, and that the HfO_2 could not be in an anti-prismatic lattice arrangement because of the observed non-zero effective field gradient. It is apparent that TDPAC data can give information on chemical structure and bonding, and should allow rather detailed understanding of structural and symmetry questions.

F. Geosciences

Investigation of the isotopic abundance of various elements plays a significant role in geophysics and geochemistry. Possibly the best known reason is that isotope ratios provide a sensitive means of identifying the ages of geological objects. Another reason is that many chemical processes exhibit isotope effects[91] which modify physical properties (vapor pressure, melting point, etc.) and chemical properties (reaction rates). As a consequence, different isotopic ratios can develop in a sample, depending on its history. In addition, there is the interesting question of whether the isotopic abundance of elements on earth is the same elsewhere in the universe. The study of meteorites is particularly informative in this regard, as are the study of moon samples and data from the Viking mission to Mars. Lunar measurements, for example, show fairly large enrichments of the heavy isotopes of various light elements, e.g., ^{13}C, ^{15}N, ^{18}O, ^{30}Si, ^{34}S, and ^{41}K. The present view[121] is that these enrichments are related to preferential loss of the lighter isotopes caused by alternate vaporization-condensation cycles due to particle bombardment from the solar wind. Similarly, the enrichment of ^{15}N in the Martian atmosphere is nearly twice what it is on earth; this is attributed to selective escape of ^{14}N.

Table VI shows the use of separated isotopes in the geosciences during the last three years. Although a substantial number of different isotopes are

required, the amounts of each needed by a given research group are invariably quite small, 1-50 mg amounts being the norm. Essentially all of the isotopes are utilized for the same purpose, that is, as "spikes" in the IDMS method (see Sec. II-D). This technique, described in Ref. 100, is the standard method of doing accurate quantitative isotope mass spectrometry. In addition to the isotopes listed in Table VI, uses were reported for gaseous separated isotopes not covered here, including $^{17,18}O$, ^{34}S, $^{36,38}Ar$, Kr, and Xe. Here too only small amounts will probably be needed. A few illustrations of the uses for isotopes in geoscience research appear below.

Radiological Dating

Radiological dating is the technique used to determine the age of various geological objects. In order to obtain an absolute chronology, time measurements should be based on a process which has been occurring at the same rate throughout the earth's history.[122] Radioactivity is the only known process which meets this requirement. The dating of very old objects requires a radioactive decay with a comparably long half-life. Fortunately, there are several isotopes which have half-lives of 10^9-10^{11} years (the age of the earth being about 6×10^9 years[122]) and are therefore suitable for this purpose. [Assuming that such long half-life nuclides as $^{238}U(4.5\times10^9$ y), $^{232}Th(1.4\times10^{10}$ y), $^{147}Sm(1.1\times10^{11}$ y), $^{87}Rb(4.8\times10^{10}$ y), and $^{40}K(1.3\times10^9$ y) are not currently being produced in nature, this time scale provides a rough upper limit for the age of the universe.]

Dating methods based on most of these long-lived isotopes are being used at present. The methods based on ^{232}Th and ^{238}U decay are not always completely reliable because of the poorly defined isotopic ratios for Pb, which have to do with the fact that both radiogenic and non-radiogenic Pb exist in nature. In the recent literature, the two most generally used dating schemes involve $^{40}K/^{40}Ar$ and $^{87}Rb/^{87}Sr$. Both of these techniques obtain a date for an object by measuring, with a mass spectrometer, the ratio of atoms of the two species in it, and then connecting this to a time via the radioactive decay laws.[122] The $^{40}K/^{40}Ar$ technique requires ^{38}Ar of very high purity to use as a "spike" to obtain the absolute ^{40}Ar content via IDMS. (This material is apparently obtained entirely from foreign suppliers

at the present time.) The $^{87}Rb/^{87}Sr$ method of dating various mineral samples is illustrated in Refs. 123 and 124. In Ref. 124 the results for certain samples were cross-checked against the $^{40}K/^{40}Ar$ technique. In general the agreement was satisfactory, but it was suspected[124] that the ages obtained by both techniques (up to 500 million years) were too low in some cases, because the Sr had been leached from the samples and some of the Ar had escaped. Nonetheless, the $^{87}Rb/^{87}Sr$ technique appears in most cases to yield reliable chronological information.

Isotopic Anomalies

As mentioned earlier, one question of interest to geoscientists is whether the isotopic ratios found on earth are consistent with those found in extraterrestrial materials. Wasserburg and coworkers at the California Institute of Technology have studied this question for various isotopes of uranium,[125] titanium,[126] and silver[127] in meteorite samples. No anomalies were found in the $^{235/238}U$ ratio, although some had been reported earlier. The conclusion was that the earlier samples were contaminated with ^{235}U from a spike solution. (Chen and Wasserburg[125] avoided this problem by making up a $^{233}U/^{236}U$ double spike instead.) In the case of the titanium isotopes, however, significant anomalies were found, especially in the very neutron excess isotope ^{50}Ti (also ^{48}Ca). Based on all of their data, the researchers at Cal Tech concluded that the isotopic ratios were probably explainable only by assuming that several different nucleosynthesis processes were involved in the production of these nuclides. Finally, analysis of the Santa Clara and Pifion meteorites has shown an anomalous $^{107}Ag/^{109}Ag$ ratio, ranging from 1.7 to 2.8, compared with a normal value of 1.09. The data are consistent with the "extra" ^{107}Ag arising from decay of ^{107}Pd, but the possibility of an intense local cosmic ray irradiation production mechanism cannot be excluded.

Table 1

Usage of Electromagnetically Separated Stable Isotopes and Derived Radioisotopes in Nuclear Physics/Chemistry. The amounts shown represent usage (in mg) for the 3-year period, 1979-1981.

H		(a)
He		(a)
Li		
	6	7,400,000
	7	297,000
Be		
	9	(b)
B		
	10	5,300,000
	11	176,000
C		
	12	1600
	13	189,000
N		(a)
O		(a)
F		
	19	(b)
Ne		(a)
Na		
	23	(b)
Mg		
	24	3600
	25	160
	26	41,000
Al		
	27	(b)
Si		
	28	3000
	29	155,000
	30	56,000
P		
	31	(b)
S		
	32	600
	34	1100
	36	100
Cl		
	35	200
	37	100
Ar		(a)
K		
	40	300
	41	2
Ca		
	40	74,000
	42	1300
	43	300
	44	73,000
	48	22,000
Sc		
	45	(b)
Ti		
	46	1000
	48	300
	50	800
V		
	51	200
Cr		
	50	700
	52	60,000
	53	60,000
Mn		
	55	(b)
Fe		
	54	228,000
	56	17,000,000
	57	1100
	58	600
Co		
	59	(b)
Ni		
	58	330,000
	60	182,000
	62	41,000
	64	43,000
Cu		
	63	175,000
	65	175,000
Zn		
	64	1300
	66	500
	67	200
	68	800
	70	110
Ga		
Ge		
	70	1000
	72	800
	74	700
	76	100
As		
	75	(b)
Se		
	76	5500
	78	450
	80	450
	82	41,000
Br		
Kr		(a)
Rb		
Sr		
	84	100
	86	3100
	87	110,000
	88	51,000
Y		
	89	(b)
Zr		
	90	750
	91	350
	92	700
	94	700
	96	700
Nb		
	93	(b)
Mo		
	92	2900
	94	600
	95	200
	96	450
	98	1200
	100	1700
Tc		(c)

Table 1, cont.

Ru		
	96	550
	98	100
	99	100
	100	350
	101	100
	102	100
	104	300
Rh		
	103	(b)
Pd		
	102	500
	104	75
	105	20
	106	75
	108	600
	110	350
Ag		
	107	350
	109	300
Cd		
	106	2000
	110	10,000
	111	10,000
	114	200
In		
Sn		
	112	1400
	116	31,000
	118	32,000
	119	200
	120	210,000
	122	32,000
	124	33,000
	126	250
Sb		
Te		
	120	100
	122	350
	124	300
	125	6000
	126	300
	128	300
	130	6000
I		
	127	(b)
Xe		(a)

Cs		
	133	(b)
Ba		
	134	10,000
	135	200
	136	200
	138	150
La		
Ce		
	136	10,000
	140	400,000
	142	100,000
Pr		
	141	(b)
Nd		
	142	120,000
	143	50,000
	144	600
	145	51,000
	146	80
	148	110
	150	74,000
Pm		(c)
Sm		
	144	2000
	147	800
	148	1200
	149	700
	150	450
	152	2100
	154	3800
Eu		
	151	650
	153	150
Gd		
	152	8500
	153	35,000
	155	21,000
	156	212,000
	157	130,000
	158	1200
	160	2000
Tb		
	159	(b)
Dy		
	162	59,000
	163	50,000
	164	51,000

Ho		
	165	(b)
Er		
	162	250
	164	200
	166	40
	167	6000
	168	52,000
	170	250
Tm		
	169	(b)
Yb		
	171	190,000
	173	300
	174	1000
	176	500
Lu		
	176	300
Hf		
	176	100
	180	650
Ta		
	180	160
W		
	180	550
	182	51,000
Re		
Os		
	184	10
	186	3000
	187	3000
	188	50,000
	189	50,000
	190	52,000
	192	52,000
Ir		
	191	2300
	193	2300
Pt		
	192	15,000
	194	2000
	195	2000
	196	500
	198	2800
Au		
	197	(b)

Table 1, cont.

Hg		Np		At	(c)		
196	150	237	100,000	Rn	(c)		
200	2000	Pu		Fr	(c)		
204	650	239	140,000	Ra	(c)		
205	1000	240	51,000	Ac	(c)		
Tl		244	3500	Th			
Pb		Am		232	360,000		
204	8500	Cm		Pa			
206	41,000	248	1	U			
207	100	Bk		233	100,000		
208	550,000	249	1	234	16,000		
Bi		Cf		235	940,000		
209	(b)	249	1	236	30,000		
Po	(c)			238	710,000		

Notes: (a) Stable isotopes used in research, but not separated electromagnetically.
(b) Mono-isotopic in nature.
(c) No stable isotopes exist.

Table II

Usage of Electromagnetically Separated Stable Isotopes and Derived Radioisotopes in Medium Energy Physics. (The amounts shown represent usage (in mg) for the 3-year period, 1979-1981.

Li		Fe		Sn				
	6	810,000		54	7300		112	7000
	7	810,000		56	1300		116	7000
B		Ni					118	70,000
	10	60,000		58	210,000		120	37,000
	11	60,000		60	7500		122	6000
C				62	6000		124	12,000
	12	10,000		64	6000	Te		
	13	320,000	Cu				125	20,000
	14	50,000		63	500	Sm		
Mg		Zn					144	500
	24	40,000		64	2		148	500
	25	40,000	Ge				150	20,000
	26	142,000		72	6000		152	500
Si				76	500		154	6000
	28	20	Se			Gd		
	29	1000		76	500		155	21,000
	30	22,000	Sr			Dy		
S				87	2000		161	18,000
	32	500		88	2000	Er		
	34	6000	Zr				166	6000
Ca				90	84,000	Yb		
	40	20,000	Mo				176	6000
	42	180,000		92	40,000	Hf		
	44	26,000	Ru				177	25,000
	48	29,000		100	5000	Ta		
Ti				104	5000		181	10
	48	200,000	Pd			Pb		
	50	50,000		110	10,000		204	3000
V		Cd					206	3000
	51	10		110	50,000		207	170,000
Cr				111	50,000		208	115,000
	50	300		112	50,000	U		
	52	41,000					238	2
	54	300						

Table III

Usage of Electromagnetically Separated Stable Isotopes and Derived Radioisotopes in Radiochemistry. The amounts shown represent usage (in mg) for the 3-year period, 1979-1981.

Li	
6	223,000
7	1,000,000
B	
10	5000
Ca	
48	4000
Ti	
48	2000
Fe	
57	500
58	50
Cu	
63	376
65	1920
Zn	
68	20
Mo	
92	500
96	500
100	700
Ru	
96	10
Ag	
109	50
Cd	
106	10
108	10,000
Sn	
116	2000
118	50
120	2000
124	200
Te	
130	500
Ce	
140	300
Nd	
146	200
148	200
150	1
Sm	
144	700
148	200
149	200
150	250
154	400
Eu	
151	200
153	200
Yb	
170	100
176	300
Lu	
176	300
Hf	
172	2
176	10
177	10
179	20
180	10
W	
180	2
Ir	
191	5
192	5
Pt	
198	15
Pb	
208	5900
Th	
230	10
U	
233	200
235	75
238	50
Pu	
239	5
242	1
244	5

Table IV

Usage of Electromagnetically Separated Stable Isotopes and Derived Radioisotopes in Other Chemistry. The amounts shown represent usage (in mg) for the 3-year period, 1979-1981.

Li		
	6	10,000
	7	10,000
B		
	10	5500
	11	500
C		
	13	61,000
Si		
	29	5100
Ti		
	47	400
Cr		
	50	1000
	53	1200
Fe		
	56	8100
	57	1600
Co		
	57	1
Cu		
	63	200
	65	1500
Sr		
	87	500
Mo		
	95	300
Nd		
	142	50
	144	50
	146	50
	148	50
Dy		
	164	100
Er		
	167	100
	170	200
Yb		
	171	200
W		
	183	4200
Hg		
	200	100

Table V

Usage of Electromagnetically Separated Stable Isotopes and Derived Radioisotopes in Other Physics. The amounts shown represent usage (in mg) for the 3-year period, 1979-1981

Li		Sb	
	6	180,000	123	100
	7	380,000	125	100
B		Te	
	11	10,000	126	200
C		Sm	
	13	2200	154	200
Mg		Eu	
	24	100	151	10
Fe		Gd	
	56	1000	160	400
	57	2800	Dy	
Co			160	200
	60	700	Er	
Ni			168	200
	58	100	Yb	
	60	50	172	1500
Zn		W	
	67	10	180	10
Se		Hg	
	77	500	198	100
Mo			199	10
	92	70	200	200
	94	70	201	100
	95	70	202	100
	96	70	204	6
	97	70	Tl	
	98	70	203	500
	100	70	Pb	
Tc			207	300
	99	3000	U	
Ag			235	1000
	107	50	Am	
	109	1000	241	5000
Cd			243	2000
	114	500	Cm	
Sn			244	500
	118	260		
	119	1000		

Table VI

Usage of Electromagnetically Separated Stable Isotopes and Derived Radioisotopes in Geosciences. The amounts shown represent usage (in mg) for the 3-year period, 1979-1981.

Li	
6	30
7	30
B	
10	30
11	30
Mg	
24	30
25	31
26	1
Si	
29	750
30	.0
K	
40	210
41	800
Ca	
42	500
43	100
44	6
48	100
Ti	
50	30
V	
50	30
Cr	
50	30
53	30
54	30
Fe	
54	30
57	30
58	30
Ni	
62	30
64	30
Zn	
64	1
66	1
67	30
70	31
Rb	
87	850
Eu	
151	41
153	1
Gd	
155	2
157	10
158	30
160	30
Dy	
160	30
161	2
Er	
164	30
167	2
Yb	
170	30
171	2
176	30
Lu	
176	41
Hf	
179	40
Tl	
203	31
205	1
Pb	
204	31
205	130
206	250
207	30
208	450
Th	
230	31
U	
233	30
234	30
235	5
236	30
Sr	
84	750
86	260
Zr	
91	30
96	30
Pd	
102	30
108	30
110	30
Ag	
107	30
109	30
Cd	
106	30
108	1
111	1
113	1
Sn	
118	1
120	1
Ba	
134	30
135	1
136	400
137	30
La	
138	41
Ce	
138	30
142	42
Nd	
145	43
148	30
149	1
150	70
Sm	
144	30
147	60
149	15
150	30

III. STABLE ISOTOPE SUPPLY PROBLEMS

As part of the survey (see Appendix A), respondents were asked to indicate whether they had experienced any problems or significant delays in obtaining isotopes. Some 26% of the respondents in all categories answered in the affirmative. These problems should not be taken as a reflection on the ORNL personnel working in the Stable Isotope Sales area, who were specifically praised for their cooperation. The breakdown of the responses by research category is shown in Table VII; there is some tendency for the major isotope users to have a larger percentage of the difficulties.

Reported problems can be grouped into four main areas: unavailability of isotopes, marginal enrichment or chemical purity, delays in obtaining isotopes, and high cost. Disturbingly, nearly half of the respondents reporting a problem (12% of all respondents) found certain isotopes unavailable. Particular isotopes that were specified as being unavailable or having too low enrichment included ^{26}Mg, $^{29,30}Si$, ^{50}Ti, ^{67}Zn, ^{77}Se, ^{84}Sr, ^{96}Ru, ^{110}Pd, ^{113}Cd, $^{112,118,124}Sn$, ^{134}Ba, ^{138}La, ^{150}Nd, $^{154,160}Gd$, ^{176}Lu, ^{180}W, $^{189,190}Os$, ^{191}Ir, ^{198}Pt, ^{201}Hg, and ^{233}U.

The lack of sufficiently enriched materials is becoming a particularly serious problem. Although many isotopes are technically "in stock," they are of marginal utility to the research community because of low enrichment or unacceptable chemical contaminants. A notable example of insufficient enrichment is ^{84}Sr, which is heavily used in geochronometry. Until recently, the National Bureau of Standards provided this isotope as a high-purity Standard Reference Material (SRM-987 to its friends), but it is no longer available. In practice, replacing material of >95% isotopic purity with material from ORNL having only 82% purity introduces significant uncertainties into the IDMS technique discussed in Secs. II-D and II-F. For

most, if not all, of the fields considered in this paper, there is a distinct tendency to require the highest isotopic purity of the most rare isotopes -- both neutron-poor and neutron-rich -- since these frequently lead to the most unusual products in a nuclear reaction or provide the least potential interference in mass spectrometry measurements. As a consequence of the lack of highly enriched isotopes, several groups have had to resort to the tactic of purchasing a low-enrichment isotope and having it further enriched on a colleague's isotope separator, or, in the case of ^{38}Ar, purchasing all of their supplies of >99% enriched material from a foreign (Swiss) supplier. This is both inefficient and time consuming, and is clearly impractical as a long-term solution to the basic difficulty.

A number of respondents reported a complete lack of availability of certain separated isotopes. Nearly 5% of the researchers indicated that they had abandoned at least one planned experiment in the past three years due to inability to procure the requisite material. Although this number is not (presently) overwhelming, one cannot help but make an analogy to the failure of a string of resistors: each time one fails, the load on the rest increases until the next weakest one goes, and so on.

Although these materials were only out of stock temporarily, rather than forever, there is often not much difference as far as basic research is concerned. In some fields of research, e.g., high energy physics, a particular experiment may take 5 years or more from conception to completion, but for most of the fields considered in this document the time scale is much shorter. Thus, the unavailability of a particular enriched isotope for a period of several years very likely means that the experiment is, to all intents and purposes, dead. [At many major nuclear physics facilities a "scheduling cycle" for a series of approved experiments is 4-6 months; experiments not completed within one year from the date of the original proposal are considered sufficiently out of date that they are automatically "removed from the books."] Furthermore, in nuclear physics and nuclear chemistry, which dominate the research usage of enriched isotopes, there is a tendency to exhibit "resonance-like" purchasing patterns. A newly discovered phenomenon such as backbending caused a resonance in rare earth purchases, while the ALAS phenomenon in $^{16}O + {}^{28}Si$ scattering generated a resonance

in Mg and Si purchases (for both of which the heavier isotopes are now out of stock). It would seem best to deal with such fluctuations by having enough material on hand to average them out over a period of several years. As of now this is obviously not happening, since in July 1981 there were 65 isotopes reported to be out of stock.

Fortunately, much of the research with large requirements for enriched isotopes --neutron, photonuclear, pion, electron, and double beta decay experiments-- can do nicely with target materials loaned from the Research Isotopes Pool at ORNL. The results of the survey indicate that this part of the system is functioning reasonably well. Occasional delays occur when an isotope is signed out, but it seems that the scientists concerned are generally able to negotiate directly to arrive at a mutually satisfactory solution. Since the number of respondents worried about the availability of pool isotopes is roughly balanced by those who already have isotopes and are worried about how long they can keep them, the system seems to be in equilibrium. Of course, these isotopic targets are fairly rugged and can presumably be used many times without incident. [Targets for the majority of nuclear physics experiments, however, tend to be thinner and more fragile, and are frequently destroyed by interactions before, during, or after the experiment, e.g., interactions with fingers, screwdrivers, or occasionally malevolent vacuum systems. Insofar as these items are a routine part of most experimental setups, this problem will remain with us.]

With respect to costs, the one issue raised repeatedly was the astronomical cost of ^{48}Ca. Because of its large N/Z ratio, this isotope is prized in many experiments, ranging from the search for superheavy elements to studies of nuclear matter radii with pions. For many projects a comparison of the behavior of ^{40}Ca and ^{48}Ca is the most straightforward way to elucidate nuclear structure effects, but the high cost of ^{48}Ca has begun to price the scientific community out of the market. Other statements regarding isotope costs must be "normalized" to some extent. At one extreme there were comments about the expense of having to order a "special calutron run" to produce a needed isotope, while at the other extreme one user commented that his "entire research budget would not cover the interest on the loan" to acquire a particular isotope. Nonetheless,

the problem of excessive and rapidly rising costs for some isotopes is real and must be dealt with somehow. If special calutron runs were to become the rule, rather than the exception, the entire community of isotope users would clearly suffer.

As mentioned above, some researchers have been forced to abandon certain experiments due to the lack of suitable materials. Others have been able to solve their problems, at least temporarily, by borrowing targets or enriched materials from colleagues at other institutions. Although one researcher tried "ordering well in advance," within the limited statistics of the present survey we find that this approach is not in wide use. A majority of respondents appears to have adopted the "begging and waiting" approach. One isotope user claimed to have solved his problem by "developing patience," but it seems unlikely that this will ever become a general solution for the research community.

Table VII

Reported Problems with Electromagnetically Separated Isotope Supplies

Category	Unavailable[a] (%)	Enrichment[a] (%)	Delays[a] (%)	Cost[a] (%)	Total[a,b] (%)
Nuclear Physics	13	6	20	4	43 (14)
Medium Energy Physics	23	4	-	-	27 (2)
Radiochemistry	16	11	5	5	37 (2)
Other Chemistry	4	2	4	4	14 (3)
Other Physics	4	6	1	1	12 (2)
Geosciences	16	4	-	9	29 (3)
Totals	(12)	(4)	(6)	(4)	(26)

a) Each number refers to the percentage of the total responses in that category only - values in different categories are not directly comparable.

b) Numbers in parentheses are the percentage of total responses from all six categories.

IV. TRENDS IN FUTURE SEPARATED ISOTOPE REQUIREMENTS

In this section, we will look at how the various uses of stable isotopes are expected to change in the next 5 years, and at how such changes will affect the demand for separated stable isotopes. In a similar survey[128] on stable isotopes which was carried out by a National Research Council panel in 1968, it was stated that "since nuclear structure, spectroscopy, and reaction studies are concerned with the systematics of all the isotopes of an element, separated samples of nearly all isotopes have been and continue to be required." The present investigation (see Tables I-III) shows that this is still the case. Of the elements between hydrogen and bismuth which have more than one isotope, all but eight were utilized for nuclear science experiments in the past three years. (If one includes the other research areas covered here, for which isotope utilization is shown in Tables IV-VI, only separated isotopes of Ga, Br, In, and Re were not used during this period.) The overall amounts used, along with their approximate costs, are summarized in Table VIII. (Some attempt was made to estimate and exclude the non-destructive uses in determining these costs.)

Because of the manner in which basic research is carried out, it is at best difficult to make predictions of future needs in a quantitative fashion. For this reason, no attempt will be made here to provide detailed numerical estimates for each isotope. Rather, we will look at the trends in scientific programs and comment on areas where significant changes in isotope usage are likely. One of the topics covered in the survey was expected future needs, especially where they might differ from present needs. The survey showed a surprisingly uniform attitude in all six research areas. There was a clear consensus that research needs for stable isotopes would be approximately constant during the next 5-year period. (Even those who felt

that changes would occur indicated that such changes would be "slight" or "moderate.") This does not mean, of course, that the research itself will be the same, since it is clear that there will be changes in the mix of such isotopes and the experiments for which they will be used.

First, let us consider the field of nuclear physics/chemistry, which has historically been (and is likely to continue to be) the largest user of stable isotopes for basic research purposes. In the next 5 years, it seems probable that nuclear physics will continue an evolution that, to some extent, parallels that of high energy physics. Historically, nuclear physics has been carried out at a large number of facilities, mainly situated on university campuses, and has involved a correspondingly large number of independent research groups, each with its own professor, perhaps a few postdoctoral scientists, and several graduate students. More recently, however, the trend has been toward fewer but larger facilities (in terms of beam energy and availability of experimental equipment). Thus, nuclear physics has entered the "user" phase of its evolution. Much can be said about whether this is good or bad, but it is nonetheless a reality. This has several effects on the way nuclear physics is done. One of the most obvious is the shrinkage in the amount of beam time allotted to each research group. Because many of the smaller facilities are being closed, researchers now find it increasingly necessary to formally submit proposals for beam time, have them approved, and then schedule time on an accelerator which may be hundreds, or even thousands, of miles away from their home laboratory. In practice, this tends to mean that a group will perform fewer experiments per year, although an individual experiment may be longer than was the case previously. Thus, a research group uses fewer targets per year, but performs more sophisticated measurements on each. It is also true that most major facilities (e.g., the Holifield Heavy Ion Research Facility at ORNL, the Brookhaven Tandem Van de Graaff Laboratory, the LBL SuperHILAC) are considerably oversubscribed.

Several patterns are evident in experimental nuclear physics programs. One is a general trend toward heavier projectiles and higher beam energies. This will have an effect on allowable target thicknesses such that more material per target will become the rule. [Of course, this statement refers mainly to the relatively thin targets used in heavy ion experiments; for

neutron, electron, or pion work, a restriction on target thickness would not be coupled to the beam energy.] In addition, there has been considerably more emphasis on investigating rare processes which, because of their low cross sections, require thicker targets to achieve acceptable counting rates. With regard to choice of targets (which have always made up the bulk of the separated isotope usage for nuclear physics), the clear consensus in the research community is that it is impossible to predict exactly which isotopes will be needed in the future. Nonetheless, some general points did emerge from the survey.

The rare earth isotopes will remain in high demand, since they have regularly provided us with the most exciting and surprising information on nuclear structure. Other materials which seem likely to keep their high appeal are those with a wide range of available isotopes, such as Ca, Ni, Zr, Mo, Sn, Sm, and Pb. These isotopes allow the exploration of changes in nuclear structure and reaction mechanisms due to changes in N/Z ratio, distance from closed shells, and deformation. There is also likely to be a considerable demand for isotopes in the Mg-Si region. This mass region has shown evidence for interesting but as yet poorly understood structures which will undoubtedly be investigated in more detail. We have already noted, however, that many of these isotopes are now out of stock and may not be available for several years - a clearly unfortunate situation! In general terms, it is probably safe to say that targets of isotopes on the extremes of the mass distribution for any element (i.e., both neutron-rich and neutron-poor species) will be in demand, since these offer the best possibilities for producing nuclei far from beta stability and studying their properties. At UNISOR, for example, there is a need for the lightest isotopes of all refractory elements for producing neutron-deficient nuclei. Finally, it can be predicted that the demands for radioactive targets will continue to expand. In general, the amounts needed for the above targets will be similar to current needs, i.e., about 500-1000 mg per isotope for thick targets or about 50-100 mg per isotope for very thin targets.

As in the past, a crucial aspect of the targets will be their enrichment. In most cases the addition or removal of even a single neutron can have a significant effect on a nuclear reaction. Moreover, the problem of

competing reactions with an isotopically mixed target leads to background processes which almost invariably obscure the reaction of interest (or at least make its analysis complicated and ambiguous). Unfortunately, this tends to be especially true for the isotopes on the extremes of the mass distribution, e.g., ^{48}Ca or ^{112}Sn, whose natural abundance is low. Thus, the isotopes of the lowest natural abundance are just the ones for which very high isotopic purity (>95%, and preferably >99%) is most crucial. The lack of high purity rare isotopes is a weakness in the present supply system that must be corrected.

Another clear trend in heavy ion experimental programs is that new accelerators just coming on-line will all have the capability of accelerating relatively heavy beams to energies well above the Coulomb barrier on most targets. (The SuperHILAC, and Michigan State University Phase II when completed, will do so with any mass ion, while HHIRF and Atlas will do so for ion masses up to about 160 and 130, respectively.) This will stimulate the use of stable isotopes as exotic projectiles, a use that has only recently begun to be exploited. It is clear that the most interesting choice for a projectile is ^{48}Ca, followed by several other neutron-rich ions, such as ^{26}Mg, ^{30}Si, ^{36}S, ^{50}Ti, ^{58}Fe, and ^{64}Ni. These ions allow studies of nuclei far from the valley of beta stability, in relatively unknown territory as far as nuclear structure goes. The use of stable isotopes for beams implies that the quantities required will increase significantly. It is likely that 1-5 g amounts of many of the isotopes just listed will be needed at various accelerators. Based on the experience at the SuperHILAC, which for many years has been accelerating ^{48}Ca beams as well as enriched beams of ^{86}Kr and ^{136}Xe, it is possible to recover a substantial portion of the rare isotope if proper care is taken in the design of the ion source and its attendant vacuum system. (Approximately 80% of the ^{48}Ca isotope in the source is recoverable at the SuperHILAC.) In addition, it should be recognized that the requirement for isotopic purity is much less severe when the material is used to provide a beam than when it is used as a target. This is because most accelerators have reasonably good mass separation properties, thereby allowing only the isotope of interest to be accelerated. In fact, once the enrichment gets much beyond 50% the law of diminishing returns comes into play, in the

sense that a further increase in enrichment to 99% improves the beam intensity by only a factor of two. The 70-80% enrichments provided by ORNL for some rare isotopes are ideal from this point of view.

Separated isotopes, particularly $^{6,7}Li$, ^{10}B, and ^{56}Fe, are also expected to be required in large quantities for the fabrication of special shielding, collimators, and filters for neutron experiments. In these applications, kilogram amounts are often utilized. Also emphasized in neutron work will be studies of structural materials, such as Cr, Fe, and Ni (for which 100 g samples will be employed), and studies of stable fission products and actinide nuclei, such as $^{239-244}Pu$ (which will utilize about 1 mole of each nuclide in metallic form). An expected increase in resonance-averaged neutron capture studies (relative to thermal neutron work) will correspond to greater needs for 10-50 g samples. Here too, there will be a tendency to shift the experimental emphasis to species of lower abundance.

In medium energy physics, the demand for rare isotope targets will continue to grow. Studies of exotic reactions on isotopes at the [illegible]s of stability, for example with (π^+,π^-), (π^-,π^+), and (π^-,p) reactions, require 100 g quantities of material. For electron scattering and pion/muon work, radioactive targets such as ^{41}Ca and ^{205}Pb will be of interest. It should be mentioned here that facilities such as the Bates Linear Accelerator and LAMPF generally have a substantial library of targets on hand. Because of the large mass and "structural stability" of targets used at these accelerators, they can be shared by many groups. Stockpiles also exist in the nuclear physics community, most notably at some of the national laboratories and larger university facilities. The difference in this case, however, is that the amounts of material available tend to be rather small, say 50-100 mg quantities of materials scattered throughout the periodic table, and do not form much of a hedge against supply shortages at ORNL.

Radiochemistry research will require substantial amounts of ^{48}Ca (at least 10 g) in the future for use as a projectile in the search for superheavy elements. Also needed for this purpose are actinide and transactinide target materials, but due to their highly radioactive nature the amounts required (<1 mg) will not be large in an absolute sense. Clearly, however, the discovery of positive evidence for the existence of SHE's could be expected

to increase demand for the above nuclides. Another area where stable isotopes will continue to be in demand is in the production of various radioactivity standards for the NBS; particular isotopes mentioned in this regard are ^{104}Ru and ^{107}Ag. NBS provides Standard Reference Materials of more than 60 radionuclides at present, and the list will no doubt continue to expand.

Utilization of separated isotopes in chemistry includes experiments with NMR, ESR, and mass spectrometric techniques. It is likely that the need for electromagnetically separated isotopes in NMR work will increase in the next several years, particularly for ^{29}Si, ^{43}Ca, ^{57}Fe, ^{61}Ni, ^{63}Cu, ^{67}Zn, ^{77}Se, ^{95}Mo, ^{99}Ru, ^{113}Cd, ^{123}Te, ^{183}W, and ^{187}Os. These isotopes will be used in amounts of about 0.1-1.0 g at many NMR facilities, which are routinely involved in studies of newly synthesized compounds, heterogeneous catalysts, organo-iron compounds, etc. Although the sensitivity of NMR devices for natural abundance materials has increased substantially, the range of experimental activities has more than kept pace. Thus, many important experiments will continue to require the enhanced signals from isotopically enriched samples. For ESR measurements, ^{63}Cu will be in demand for analysis of protein structures; in addition, various complexes will be investigated with isotopes of ^{47}Ti, ^{53}Cr, ^{95}Mo, and ^{183}W, in amounts on the order of 100 mg each. (Much of this work is aimed at biomedical questions and will be covered in detail elsewhere.)

Mass spectrometric experiments will continue to require very high purity (>99%) "spike" solutions for quantitative isotopic analyses. For example, analysis of nuclear fuel elements will require ^{236}Np for measurements of ^{237}Np, ^{233}U for measurements of ^{235}U, and ^{97}Tc (produced from enriched ^{96}Ru) for determination of ^{99}Tc. A wide variety of isotopes will also be needed to monitor fission products. In general, the needs for mass spectrometric analysis in geological and environmental work will also continue to grow, and accompanying this growth will be new requirements for isotopically pure materials. The quantities involved in such work are small, however; only microgram quantities are needed for any particular analysis, and 50 mg of material can last for several years.

Isotope usage in solid state and atomic physics does not appear to be

expanding substantially at present. In Mössbauer spectroscopy the primary source will continue to be ^{57}Co (produced from ^{57}Fe), although ^{119m}Sn (produced from enriched ^{118}Sn), ^{181}Ta (produced from enriched ^{180}W), and several other sources will undoubtedly be used. The magnitude of present needs is indicated in Table V. One area where some expansion may occur is in neutron scattering studies of condensed matter. Appropriate substitution of isotopes can change the scattering lengths and make it possible to separate the contributions to the neutron scattering from different components of the material. Isotopes which may be needed here include ^{10}B, along with various Ni and Se isotopes in quantities of 10-100 grams.

Laser spectroscopic investigations of isotope shifts benefit most from the study of a range of isotopes. Thus, it is likely that such candidates as Zr and Mo isotopes will be subjects for this type of study. Other candidates for future studies include $^{107,109}Ag$, ^{113}In, ^{198}Hg, ^{203}Tl, and $^{204,207}Pb$, in amounts on the order of tens of milligrams each.

The primary use for electromagnetically separated isotopes in the geosciences will be for the IDMS technique discussed earlier. (Other needs for isotopes will arise in the study of various fractionation processes, but such studies tend to utilize mainly the lighter elements such as oxygen, nitrogen, and sulfur, which do not come from ORNL.) Specific future needs will probably include standards of ^{149}Sm and ^{145}Nd for the Sm/Nd dating method, ^{205}Pb for the U/Pb method, and ^{175}Lu and $^{174,177}Hf$ for the Lu/Hf method. Once again, the technique of mass spectrometry does not require large amounts of material, but isotopic purity can be dominant in determining the absolute error of a measurement.

Although it is not a primary concern of this report, the future costs of separated isotopes will obviously be relevant to how extensively they are used. The price of ^{48}Ca was discussed in Sec. III as an example of how a very useful isotope is becoming virtually unusable because of its expense. In spite of tightening research budgets, however, respondents to the survey clearly indicated that, given a choice between paying much higher prices for separated isotopes or not being able to get them at all, they would prefer to pay more. This is not surprising, since virtually all respondents indicated that their research would come to a complete halt without access to stable

isotopes.

One other issue relevant to the future need for stable isotopes is the question of who will be using them. What is somewhat worrisome, at least as regards the nuclear physics community, is the downward trend in the number of both senior scientists and graduate students. This trend, which was commented on by a number of respondents, has been confirmed by the Nuclear Science Advisory Committee (NSAC) Subcommittee on Manpower, which has just completed its 1980 census of basic nuclear scientists in the United States. The subcommittee report[129] offers the following conclusions:

1) There has been an overall decline of approximately 10% in the number of basic nuclear scientists in the two years between 1978 and 1980;

2) The postdoctoral population has stayed essentially constant during this period; and

3) The graduate student population has decreased by at least 10% during this period, with the ratio of students to faculty members becoming about 1:1.

This trend is already having a negative impact on the usage of isotopes, and, if left unchecked, will have an even bigger impact in the future.

Table VIII

Summary of Isotope Usage (1979-1981)

Table	No. of Species	Gram-Atoms	Gram-Atoms[a]	Approx. Cost[b]
I	187	2213 (1824)[b]	408 (18)[b]	$ 730K
II	69	323 (251)[b]	67 (1)[b]	50K
III	53	181	0.4	400K
IV	26	8.8	5.2	35K
V	47	86	1.3	270K
VI	87	0.15	0.1	90K
	220	2812 (2351)[b]	482 (26)[b]	$1575K
		[937 (784)[b]][c]	[161 (9)[b]][c]	[$ 525K][c]

a) Excluding $^{6,7}Li$, and ^{10}B.

b) Including only "destructive" uses (which cannot be satisfied by loans).

c) Annual usage.

V. SUMMARY AND CONCLUSIONS

In this document we have presented information on the research uses for electromagnetically separated stable isotopes, and radioisotopes derived therefrom, in the broad areas of physics, chemistry, and the geosciences. The information contained in this report is based on a nationwide survey of more than 1,000 physics, chemistry, and geology departments. As has been true in past studies, we found that research use of stable isotopes is greatest in the field of nuclear physics/chemistry. However, many other research areas were also found to have significant needs for separated isotopes, including medium energy, atomic, and solid state physics; physical, inorganic, and analytical chemistry; geochronometry and isotope geology. Demand for separated isotopes in the United States has remained very substantial; of the elements between hydrogen and bismuth which have more than a single isotope, only four were not used during the three-year period covered by this report. Altogether, 220 different isotopes were utilized in the research areas of physics, chemistry, and geology, corresponding to a total amount of material of nearly 3000 gram-atoms, at a cost of almost $1.6M. Approximately 85% of the material was consumed in these experiments, while 15% was put to "non-destructive" uses.

Several problems were reported, however, in the supply of stable isotopes. The most critical of these was the complete lack of a number of important isotopes. Nearly 5% of the respondents to the survey indicated that they had recently been forced to abandon plans for at least one experiment due to an inability to obtain a required isotope. At present, the amount of time needed to generate new supplies of an out-of-stock isotope can be as long as 2-3 years, which is incompatible with the shorter time frame in which most research is carried out. On the positive side, the

Research Isotopes Pool arrangement appears to be operating reasonably smoothly, and the research community has taken great advantage of it.

Another problem is the lack of sufficient enrichment for many isotopes of low natural abundance. There is a definite trend toward increased use of nuclides at the extremes of an isotope distribution. At present these are frequently not enriched sufficiently to be useful either as targets in nuclear physics experiments or for the production of high-purity radioisotopes. It is expected, however, that these isotopes, at least up to about A=100, will also see substantial service in the production of exotic ion beams. For this use, an enrichment of 50-80% should be acceptable.

Skyrocketing isotope costs are also a matter of concern. Such important isotopes as ^{48}Ca are rapidly becoming unusable due to their high cost. In spite of this, there was a clear consensus among the respondents that the value of separated isotopes to their research is so great that, within reason, they would be willing to pay significantly higher costs in order to ensure a steady supply.

There appears to be a downward trend, at least in nuclear physics, in available research personnel. If this trend continues, it will eventually begin to have a substantial negative impact on isotope utilization. It presently appears, however, that the rate of isotope usage in the next 5 years will remain essentially constant. Of course, the particular choices will change during this period. It is expected that future emphasis will be on rare earth nuclei, most of the lighter neutron-rich isotopes, and on those elements having a large number of stable isotopes, such as Ca, Mo, Sn, and Sm. In addition, fabrication of isotopically pure shielding and filters for neutron work will take kilogram amounts of such isotopes as ^{6}Li, ^{10}B, and ^{56}Fe.

The availability of separated isotopes is absolutely essential to the continued health of much of the physics, chemistry and geoscience research in this country. We are at a crossroads in terms of our ability to provide adequate supplies of suitably enriched isotopes for the future. It is critical, therefore, that the availability of stable isotopes be improved to the point where adequate supplies exist to handle the fluctuating demands of an active research community. Not to do so will eventually mean that a large portion of the physical science research in this country cannot be performed.

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50th ANNIVERSARY 1931-1981

Appendix A
SURVEY OF ISOTOPE USAGE

Lawrence Berkeley Laboratory
University of California • Berkeley, California 94720

September 18, 1981

Dear Colleague:

In response to a request from the Office of Basic Energy Sciences (OBES) of the U.S. Department of Energy, the National Research Council is organizing a Workshop on the Applications of Stable Isotopes and Derived Radioisotopes, under the aegis of its Subcommittee on Nuclear and Radiochemistry. Basically, the OBES would like documentation from the user community on present and projected applications of, and requirements for, electromagnetically separated stable isotopes in physics/chemistry research, biomedical research, clinical medicine, and industry. One goal of the Workshop, therefore, is to generate a report which summarizes the needs for these isotopes and also makes quantitative estimates of the amounts required in the future.

As part of this effort, I have been asked to gather information on the uses of stable isotopes in the broad areas of physical and chemical research, including nuclear physics/chemistry, geophysics/geochemistry, mass spectroscopy, etc. Because of the somewhat amorphous nature of the area for which I am responsible, it is difficult to arrive at an inclusive mailing list. For this reason, **it is essential that you distribute copies of this note to any colleagues at your institution who have (or expect to have) need for either separated stable isotopes or the radioisotopes derived therefrom.**

My suggestion is that you appoint a "contact person" at your institution (perhaps a secretary) who will ensure that the enclosed questionnaire is copied, distributed, collected and returned to me. It would be helpful to have the name and phone number of this person as soon as possible; a simple form for this purpose is attached. Should there be no members of your institution who use stable isotopes in their research, please indicate this on the return form and I will delete your name from our mailing list.

Please have all your questionnaires filled out and returned to me by **October 16, 1981.** The information you provide will help the OBES ensure a continuing supply of stable isotopes in the future.

Thank you very much for your cooperation in this effort.

Sincerely,

Michael S. Zisman

Michael S. Zisman
Assistant Head
Nuclear Science Division

Telephone: (415) 486-4000 FTS 451-4000

Please return your completed questionnaire by **Oct. 16, 1981** to:

Michael S. Zisman
Building 71
Lawrence Berkeley Laboratory
Berkeley, CA 94720

Questionnaire

Applications of Stable Isotopes and Derived Radioisotopes

(Please type or print - use black ink.)

1. Name; Title

2. Institution; Mailing Address; Phone Number

3. a) Identify and describe your field(s) of research.

   b) List a few of your recent publications in the above fields.

4. a) Describe (briefly) how stable isotopes, or radioisotopes derived therefrom, are used in your research, e.g., as target materials, to produce ion beams, as tracers, etc.

b) Indicate which stable isotopes are utilized in your research and the amounts of such isotopes used in the past 3 years, e.g., ^{56}Fe (500 mg).

5. a) Where were your isotopes obtained?

b) Have you had problems with availability of required isotopes or significant delays in obtaining them? If so, how did you solve these problems?

c) Do you presently have a stockpile of separated isotopes? If so, what materials (and quantities) are included?

6. a) If you utilize radioisotopes derived from separated stable isotopes, what reactions were used for the conversion?

b) Where and by whom were the derived radioisotopes produced?

c) Indicate why separated stable isotopes must be used in the radioisotope production process, e.g., unwanted competing reaction products, etc. Be specific.

So much for the easy part. Now for the future . . .
(Please note that it is important to be realistic here; the questions below do not involve research budgets!)

7. a) Indicate the isotopes you envision using in the next 3-4 years and their amounts (as in question 4a).

b) Describe how these isotopes will be used, emphasizing differences compared with your answer to question 4. (For example, do you anticipate significantly different uses for the isotopes or radioisotopes, or significant changes [up or down] in the amounts which will be required? If so, why?)

c) How do you anticipate your needs for stable isotopes changing in the long term (beyond the next 5 years)? (Do you see your needs remaining nearly constant or increasing/decreasing significantly? Please explain.)

8. How important are separated stable isotopes or derived radioisotopes to your research? Would your research be significantly impaired if certain isotopes were temporarily or permanently unavailable, or if the prices of such isotopes were substantially higher than at present?

Congratulations! You have completed the hardest part. Now all that's left is for you to **mail the questionnaire back to me at the address given on the first page.** Thank you for your help.

Appendix B
INSTITUTIONS CONTACTED

Alabama
- University of Alabama
- University of Alabama in Birmingham
- University of Alabama in Huntsville
- Auburn University
- Tuskegee Institute

Alaska
- University of Alaska at Fairbanks
- University of Alaska at Juneau

Arizona
- Arizona State University
- University of Arizona
- Northern Arizona University

Arkansas
- Arkansas State University
- University of Arkansas at Fayetteville
- University of Arkansas at Little Rock
- University of Central Arkansas
- Ouachita Baptist University

California
- Aerospace Corp. Space Science Laboratory
- California Institute of Technology
- California Institute of Technology - Jet Propulsion Laboratory
- California Polytechnic State University at San Luis Obispo
- California State Polytechnic University at Pomona
- California State University at Fresno
- California State University at Fullerton
- California State University at Hayward
- California State University at Humbolt
- California State University at Long Beach
- California State University at Los Angeles
- California State University at Northridge
- California State University at Sacramento
- University of California at Berkeley
- University of California - Lawrence Berkeley Laboratory
- University of California - Lawrence Livermore National Laboratory
- University of California at Davis
- University of California at Irvine
- University of California - Institute of Geophysics and Planetary Physics

University of California at Riverside
University of California at San Diego
University of California at Santa Barbara
University of California at Santa Cruz
Naval Postgraduate School, Monterey
Pacific Union College
University of the Pacific
San Diego State University
San Francisco State University
University of San Francisco
San Jose State University
University of Southern California
Stanford University
Stanford University - High Energy Physics Laboratory
Stanford Linear Accelerator Center

Colorado

Atomic Physics Chemistry Laboratory, Boulder
Colorado School of Mines
Colorado State University
University of Colorado
University of Colorado at Colorado Springs
University of Colorado at Denver
University of Denver, Colorado Seminary
National Center for Atmospheric Research
University of Northern Colorado
Space Environment Laboratory, NOAA
Western State College of Colorado

Connecticut

University of Bridgeport
Central Connecticut State College
University of Connecticut
University of Connecticut - Institute of Material Science
Quinnipiac College
University of Hartford
Saint Joseph College
Trinity College
Wesleyan University
Yale University

Delaware

University of Delaware

District of Columbia

The American University
Carnegie Institute of Washington
Carnegie Institute - Geophysics Laboratory
The Catholic University of America
George Washington University
Georgetown University
Howard University
National Bureau of Standards

Florida
University of Central Florida
Florida Atlantic University
Florida Institute of Technology
Florida International University
Florida State University at Tallahassee
University of Florida
University of Miami
University of South Florida

Georgia
Albany State College
Atlanta University
Columbus College
Emory University
Georgia Institute of Technology
Georgia State University
University of Georgia

Hawaii
University of Hawaii

Idaho
Idaho National Engineering Laboratory
Idaho State University
University of Idaho

Illinois
Argonne National Laboratory
Bradley University
University of Chicago
University of Chicago Enrico Fermi Institute
DePaul University
Eastern Illinois University
Fermi National Accelerator Laboratory
Illinois Institute of Technology
Illinois State University
University of Illinois at Chicago Circle
University of Illinois at Urbana-Champaign
Loyola University of Chicago
Northeastern Illinois University
Northern Illinois University
Northwestern University
Roosevelt University
Southern Illinois University - Carbondale
Southern Illinois University - Edwardsville
Western Illinois University

Indiana
Ball State University
Butler University
Indiana State University
Indiana University
Indiana University - Purdue University at Indianapolis

University of Notre Dame
Purdue University
Rose-Hulman Institute

Iowa
Drake University
Iowa State University of Science and Technology
Iowa State University
Iowa State University - Ames Laboratory
University of Iowa
University of Northern Iowa

Kansas
Emporia State University
Fort Hays State University
Kansas State University
Kansas State University - MacDonald Atomic & Nuclear Physics # Laboratory
University of Kansas
Pittsburgh State University
Wichita State University

Kentucky
Eastern Kentucky University
University of Kentucky
University of Louisville
Murray State University
Western Kentucky University

Louisiana
Louisiana State University
Louisiana Tech University
McNeese State University
University of New Orleans
Northeast Louisiana University
Northwestern State University of Louisiana
Southern University
University of Southwestern Louisiana
Tulane University
Xavier University of Louisiana

Maine
University of Maine at Orono
Woods Hole Oceanographic Institute

Maryland
Frostburg State College
Goddard Space Flight Center
The Johns Hopkins University
The Johns Hopkins University - Applied Physics Laboratory
Loyola College
University of Maryland
University of Maryland, Baltimore County
University of Maryland, Eastern Shore

Massachusetts

Amherst College
Boston College
Boston University
Brandeis University
Bridgewater State College
Clark University
Harvard University
Harvard University - Cyclotron Laboratory
College of the Holy Cross
University of Lowell
Massachusetts College of Pharmacy
Massachusetts Institute of Technology
Massachusetts Institute of Technology - Bates Linear Accelerator Laboratory
Massachusetts Institute of Technology - Center for Space Research
Massachusetts Institute of Technology - Francis Bitter National Magnet Laboratory
Massachusetts Institute of Technology - Nuclear Science Laboratory
University of Massachusetts at Amherst
University of Massachusetts at Boston (Harbor Campus)
Mount Holyoke College
Northeastern University
Smith College
Smithsonian Astrophysics Laboratory
Southeastern Massachusetts University
Tufts University
Worcester Polytechnic Institute

Michigan

Andrews University
Central Michigan University
University of Detroit
Eastern Michigan University
Michigan State University
Michigan Technological University
University of Michigan
Northern Michigan University
Saginaw Valley State College
Wayne State University
Western Michigan University

Minnesota

Mankato State University
University of Minnesota
University of Minnesota at Minneapolis
University of Minnesota at Duluth
St. Cloud State University
Southhampton College

Mississippi
Alcorn State University
Delta State University
Jackson State University
Mississippi State University
University of Mississippi
University of Southern Mississippi

Missouri
Fontbonne College
University of Missouri - Columbia
University of Missouri - Kansas City
University of Missouri - Rolia
University of Missouri - St. Louis
Northeast Missouri State University
St. Louis University
Southeast Missouri State University
Southwest Missouri State University
Washington University

Montana
Montana College of Mineral Science & Technology
Montana State University
University of Montana

Nebraska
Creighton University
Kearney State College
University of Nebraska - Lincoln

Nevada
University of Nevada at Las Vegas
University of Nevada at Reno

New Hampshire
Dartmouth College
University of New Hampshire

New Jersey
Fairleigh Dickinson University, Teaneck
Fairleigh Dickinson University, Florham-Madison Campus
Montclair State College
Monmouth College
New Jersey Institute of Technology
Princeton University
Princeton University - Center for Environmental Studies
Princeton University - Geophysics Fluids Dynamics Laboratory
Princeton University - Plasma Physics Laboratory
Rutgers University - The State University of New Jersey
Seton Hall University
Stevens Institute of Technology
Trenton State College

New Mexico
Eastern New Mexico University
Los Alamos Scientific Laboratory
New Mexico Highlands University
New Mexico Institute of Mining and Technology
New Mexico State University
University of New Mexico

New York
Adelphi University
Brookhaven National Laboratory
PhD Program in Chemistry of the C.U.N.Y.
Brooklyn College of the C.U.N.Y.
City College of the C.U.N.Y.
Hunter College of the C.U.N.Y.
John Jay College of Criminal Justice of the C.U.N.Y.
Queens College of the C.U.N.Y.
Clarkson College of Technology
Columbia University
Cooper Union for the Advancement of Science and Art
Cornell University
Cornell University - Atomic and Solid State Physics Laboratory
Fordham University
Long Island University, Southampton College
Manhattan College
New York University
Polytechnic Institute of New York
Polytechnic Institute - Radiation Physics/Environmental Measurements Laboratory
Rensselaer Polytechnic Institute
Rochester Institute of Technology
University of Rochester
Rochester University
Saint Bonaventure University
St. John's University
S.U.N.Y. at Albany
S.U.N.Y. at Binghamton
S.U.N.Y. at Buffalo
S.U.N.Y., College of Environmental Science and Forestry
S.U.N.Y. at Fredonia
S.U.N.Y. at Geneseo
S.U.N.Y. at New Paltz
S.U.N.Y. at Oneonta
S.U.N.Y. at Oswego
S.U.N.Y. at Plattsburgh
S.U.N.Y. at Stony Brook
College of Staten Island
Syracuse University
Union College
Vassar College

North Carolina
- Appalachian State University
- Duke University
- East Carolina University
- North Carolina Agricultural and Technical State University
- North Carolina Central University
- North Carolina State University
- University of North Carolina at Chapel Hill
- University of North Carolina at Charlotte
- University of North Carolina at Greensboro
- Wake Forest University
- Western Carolina University

North Dakota
- North Dakota State University
- University of North Dakota

Ohio
- Air Force Institute of Technology (Wright-Patterson AFB)
- The University of Akron
- Bowling Green State University
- Case Western Reserve University
- University of Cincinnati
- University of Cincinnati - Laboratory of Basic & Applied Nuclear Research
- Cleveland State University
- University of Dayton
- John Carroll University
- Kent State University
- Kent State University - Lewis Research Center
- Miami University
- The Ohio State University
- Ohio University (Athens)
- University of Toledo
- Wright State University
- Xavier University
- Youngstown State University

Oklahoma
- Central State University
- Oklahoma State University
- University of Oklahoma
- The University of Tulsa

Oregon
- Oregon Graduate Center (Beaverton)
- Oregon State University
- University of Oregon
- Portland State University

Pennsylvania
- Bryn Mawr College
- Bucknell University
- Carnegie-Mellon University

Drexel University
Duquesne University
East Stroudsburg State College
Indiana University of Pennsylvania
Lehigh University
The Pennsylvania State University
The Pennsylvania State University - Applied Research Laboratory
The Pennsylvania State University - Materials Research Laboratory
University of Pennsylvania
University of Pittsburgh
Saint Joseph's University
University of Scranton
Shippensburg State College
Swarthmore College
Temple University
Villanova University
West Chester State College
Wilkes College

Rhode Island
Brown University
Brown University - Materials Research Laboratory
Providence College
Rhode Island College
University of Rhode Island

South Carolina
Clemson University
Furman University
University of South Carolina

South Dakota
South Dakota School of Mines and Technology
South Dakota State University
University of South Dakota

Tennessee
East Tennessee State University
Fisk University
Memphis State University
Middle Tennessee State University
Oak Ridge Associated Universities (UNISOR)
Oak Ridge National Laboratory
Tennessee State University
Tennessee Technological University
The University of Tennessee
Vanderbilt University

Texas
Baylor University
East Texas State University
University of Houston, Central Campus
University of Houston, Clear Lake City
Lamar University

North Texas State University
Rice University
Sam Houston State University
Southern Methodist University
Southwest Texas State University
Stephen F. Austin State University
Tarleton State University
Texas A & I University
Texas A & M University
Texas A & M University - Cyclotron Institute
Texas Christian University
Texas Tech University
The University of Texas at Arlington
The University of Texas at Austin
The University of Texas at Dallas
The University of Texas at El Paso
The University of Texas at San Antonio
Texas Woman's University
Trinity University
West Texas State University

Utah
Brigham Young University
Utah State University
University of Utah

Vermont
Middlebury College
University of Vermont

Virginia
Lynchburg College
Old Dominion University
Radford University
University of Richmond
Virginia Commonwealth University
Virginia Institute of Marine Science
Virginia Polytechnic Institute and State University
Virginia State University
University of Virginia
College of William and Mary

Washington
Central Washington University
University of Puget Sound
Washington State University
University of Washington
Western Washington University

West Virginia
Marshall University
West Virginia Institute of Technology
West Virginia University

Wisconsin
The Institute of Paper Chemistry
Marquette University
University of Wisconsin at Madison
University of Wisconsin at Milwaukee
University of Wisconsin at Oshkosh
University of Wisconsin at Superior

Wyoming
University of Wyoming

British Columbia
McMaster University
University of British Columbia

Appendix C
RESPONDENTS

Alabama

Auburn University

William L. Alford	(Physics)
John L. Aull	(Chemistry)
Philip B. Shevlin	(Chemistry)
John R. Williams	(Physics)

Arizona

Arizona State University

Devens Grust	(Chemistry)
Peter Williams	(Chemistry)

University of Arizona

James J. Knittel	(Chemistry)
Melvin Schafer	(Chemistry)
Richard Sportsman	(Chemistry)

Arkansas

University of Arkansas at Fayetteville

R. Gupta	(Physics)

California

California Institute of Technology

Felix Boehm	(Physics)
D. S. Burnett	(Geoscience)
William L. Johnson	(Physics)
R. W. Kavanagh	(Physics)
Robert T. Menzies	(Chemistry)
Marc A. Nicolet	(Physics)
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Clair C. Patterson	(Geoscience)
George R. Rossman	(Geoscience)
Leon T. Silver	(Geoscience)

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Peter B. Armentrout	(Chemistry)
Robert G. Bergman	(Chemistry)
Leo Brewer	(Chemistry)
E. Commins	(Physics)
Robert E. Connick	(Chemistry)
William G. Dauben	(Chemistry)
Charles B. Harris	(Chemistry)
Clayton H. Heathcock	(Chemistry)
Richard Mathies	(Chemistry)
Earl Muetterties	(Chemistry)
Rollie J. Myers	(Chemistry)
George C. Pimentel	(Chemistry)
P. B. Price	(Physics)
John H. Reynolds	(Physics)
Howard A. Shugart	(Physics)
Herbert L. Strauss	(Chemistry)
Andrew Streitwieser, Jr.	(Chemistry)
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Maynard C. Michel	(Chemistry)
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John Rasmussen	(Chemistry)
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David A. Shirley	(Chemistry)
G. A. Somorjai	(Chemistry)
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Robert Stokstad	(Physics)
T. J. M. Symons	(Physics)
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Richard Griffith	(Chemistry)
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Douglas A. Leich	(Geoscience)
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Paul Barrett	(Physics)
M. T. Bowers	(Chemistry)
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Mason R. Yearian	(Physics)
R. N. Zare	(Chemistry)

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George T. Furukawa	(Physics)
Dale Hoppes	(Chemistry)
John W. Lightbody, Jr	(Physics)
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Eugene H. Man	(Geoscience)

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Gus A. Petitt	(Physics)

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P. Kroopnick	(Geoscience)
John J. Naughton	(Geoscience)

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Myra D. Anderson	(Chemistry)
J. Delmore	(Chemistry)
A. L. Erikson	(Chemistry)
R. L. Tromp	(Chemistry)
Gordon W. Webb	(Chemistry)

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Robert J. Gehrke	(Chemist)
R. C. Greenwood	(Physics)
Richard G. Helmer	(Physics)
C. W. Reich	(Physics)

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Edwin House	(Chemistry)

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Danny Ashery	(Physics)
Joseph Berkowitz	(Physics)
Charles Borso	(Physics)
William T. Carnall	(Chemistry)
J. M. Carpenter	(Physics)
Partha Chowdhury	(Physics)
Cary N. Davids	(Physics)
B. D. Dunlap	(Physics)
Donald Geesaman	(Physics)
Walter Henning	(Physics)
Ben D. Holt	(Chemistry)
Roy Holt	(Physics)
Harold Jackson	(Physics)
Robert Janssens	(Physics)
Joseph J. Katz	(Chemistry)
Teng Lek Khoo	(Physics)
Dennis Kovar	(Physics)
Walter Kutschera	(Physics)
Daniel J. Lam	(Physics)
Malcolm MacCoss	(Chemistry)
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J. Norris	(Chemistry)
Karl E. Rehm	(Physics)
Martin G. Seitz	(Geoscience)
G. K. Shenoy	(Physics)
Alan B. Smith	(Physics)
Donald L. Smith	(Physics)
James Specht	(Physics)
Ellis P. Steinberg	(Chemistry)
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Sol Wexler	(Chemistry)
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Malcolm Hill	(Geoscience)

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William G. Lynch	(Physics)
D. J. Morrissey	(Chemistry)
R. H. Schwendeman	(Chemistry)
James M. Tiedje	(Chemistry)
Man-Yee B. Tsang	(Physics)
J. Throck Watson	(Chemistry)

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Jeffrey Schwartz (Chemistry)
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James B. Cumming (Chemistry)
Irving L. Feigenbaum (Physics)
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Ole Hansen (Physics)
Peter E. Haustein (Chemistry)
O. C. Kistner (Physics)
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Barry K. Carpenter (Chemistry)
David D. Clark (Physics)
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Michael E. Fisher (Chemistry)
Jack H. Freed (Chemistry)
Bruce Ganem (Chemistry)
Melvin J. Goldstein (Chemistry)
Paul Houston (Chemistry)
Fred W. McLafferty (Chemistry)
L. Que (Chemistry)
James R. Rasmussen (Chemistry)
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Olav Redi (Physics)

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W. Le Noble (Chemistry)
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George C. Levy (Chemistry)

Union College

Alfred T. Goble (Physics)

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R. L. Walter (Physics)
Chris Westerfeldt (Physics)

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Paul D. Fullagar (Geoscience)
Edward J. Ludwig (Physics)

Wake Forest University

Ysbrand Haven (Physics)

Western Carolina University

Gene F. Morris (Chemistry)

North Dakota

University of North Dakota

Glenn I. Lykken (Chemistry)

Ohio

Air Force Institute of Technology (Wright-Patterson AFB)

George John (Chemistry)

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Edgar B. Singleton (Physics)

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Willam M. Ritchey (Chemistry)

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Richard Madey (Physics)
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John Watson (Physics)

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Theodore C. Thepe (Chemistry)

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Morton Kaplan (Chemistry)
Paul J. Karol (Chemistry)

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Jack G. Kay (Chemistry)
Allan L. Smith (Chemistry)

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Peter Deines (Geoscience)
Edgar Earl Graham (Chemistry)
E. R. Vance (Physics)

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Manfred A. Biondi (Physics)
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Wilfried W. Daehnick (Physics)
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Irving J. Lowe (Physics)
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J. X. Saladin (Physics)
L. E. Seiberling (Physics)
Darel K. Straub (Chemistry)
R. W. Zurmuhle (Physics)

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Ronald G. Lawler (Chemistry)
Philip H. Rieger (Chemistry)
Michael Squillacote (Chemistry)
J. William Suggs (Chemistry)

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K. Erb (Physics)
R. L. Ferguson (Chemistry)
J. Ford (Physics)
C. Fulmer (Physics)
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M. L. Halbert (Physics)
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D. Horen (Physics)
Noah Johnson (Chemistry)
R. Novotny (Physics)
F. E. Obenshain (Physics)
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Max Hill	(Physics)
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Stanley H. Evans, Jr.	(Geoscience)
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K. Spartalian	(Physics)

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Kazuo Gotow	(Physics)
David G. I. Kingston	(Chemistry)

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Steven Brown	(Chemistry)
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K. W. Hipps	(Chemistry)
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J. A. Magnuson	(Chemistry)
K. D. McMichael	(Chemistry)
M. Pall	(Chemistry)
D. M. Roundhill	(Chemistry)
M. J. Smerdon	(Chemistry)
B. Srinivasan	(Chemistry)

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Albert I. Lazzarini	(Physics)
John Maklin	(Chemistry)
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Y. Pocker	(Chemistry)
B. S. Rabinovitch	(Chemistry)
Brian R. Reid	(Chemistry)
J. Michael Schurr	(Chemistry)
D. W. Storm	(Physics)
Robert Vandenbosch	(Chemistry)

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West Virginia University

N. S. Dalal	(Chemistry)

Wisconsin

Marquette University

Kazuo Nakamoto	(Chemistry)

University of Wisconsin at Milwaukee

James M. Cosk	(Chemistry)
Russell F. Howe	(Chemistry)
Calvin O. Huber	(Chemistry)
James T. McFarland	(Chemistry)
James Otvos	(Chemistry)
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Kenneth L. Watters	(Chemistry)

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University of Wyoming

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Ray Kunselman	(Physics)
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W. V. Prestwich	(Physics)
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APPENDIX 6

INDUSTRY NEEDS

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If one were to pick one word to describe what industry needs as far as stable isotopes are concerned, it would have to be stability -- stability with respect to supply. If one were to pick one word to describe the actual situation, it would have to be uncertainty -- uncertainty with respect to both supply and price. But I would be the first to admit that industry has brought the uncertainty onto itself, with more than a little bit of help from the Department of Energy. I do not intend to present any solutions to these problems. That should be left to the workshops, but an outline of the issues should be of help to the workshops.

For the first fifteen years that radionuclides were produced, Oak Ridge National Laboratory (ORNL) had the reactor, the cyclotron, and the Calutrons, which, along with its expertise, provided ORNL with a monopoly on production. This monopoly had at least two virtues, however. Communications between the supplier and purchasers were simplified, and uncertainties regarding supply were confined to one organization.

In the early 1960's, however, private industry began to produce radioactive isotopes for the growing field of nuclear medicine. ORNL was no longer the sole planner and scheduler, and the cost problems of commercial radionuclide producers began to influence governmental programs for the development and production of radionuclides and stable isotopes. The growth pattern changed. Industry responded to medical demands for higher specific activity and purity. As a result, ORNL found it much more difficult to predict the demand for stable isotopes. To illustrate what happened, I will concentrate on the history of three radionuclides: ^{99}Mo, ^{123}I, and ^{201}Tl.

In the 1963 ORNL catalog, ^{99}Mo was listed as being available once a week at a specific activity of greater than 10 mCi/g at prices between $1.50 and 1.00/mCi. The catalog listed the stable precursor, ^{98}Mo, at 90-99 percent concentration at $0.75/mg. At that time there was no clinical use for ^{99}Mo, but one was being developed that would dominate the field of nuclear medicine for years to come: the ^{99}Mo-^{99}Mo-^{99m}Tc generator, or "cow."

The development work on the generator was being done with fission ^{99}Mo produced at Brookhaven National Laboratory (BNL). In 1963 this

^{99}Mo was of very high specific activity but of questionable purity. The presence of somewhat unpredictable but low amounts of ^{106}Ru with low energy beta radiation and traces of alpha-emitting radionuclides was causing concern among both the regulators and the potential users of the generator. Because of this concern, the first commercial generators were made with neutron ^{99}Mo using irradiation of naturally-occurring molybenum. The low specific activity of this material dictated a low specific concentration of the ^{99m}Tc in the eluants from the early "cows," but the uses of the radionuclide in those early days did not require higher concentrations.

By 1968 the clinical applications of ^{99m}Tc were requiring higher concentrations in the eluants. This could only be achieved by using higher neutron fluxes or target material of increased ^{98}Mo content. Both methods were used. ORNL's 1968 catalog listed ^{98}Mo at \$0.20/mg, a considerable reduction from the 1963 prices of \$0.75/mg. But the demand for still higher concentrations in the eluants then began to lead to more demands for enriched stable ^{98}Mo, thus requiring more production runs at ORNL. By 1973, when the demand was greatest, the price of ^{98}Mo had risen to \$0.85/mg, and industrial producers had become concerned about their source of supply and the price of the material. In contrast to normal industrial practice, in which the price of ^{98}Mo would probably have moved up or down in small steps, ORNL was forced by governmental administrative procedures to change the price from \$0.75 to \$0.20 to \$0.85. By 1978 the price had jumped once more, to \$1.25/mg.

By that time, however, industrial users were no longer as concerned about the price. It had become apparent that fission ^{99}Mo was the only material with sufficiently high specific activity. It had become profitable to develop new processing techniques to produce an extremely high purity ^{99}Mo which no longer contained ^{106}Ru or alpha-emitting radionuclides at detectable concentration. By late 1977, all commercial ^{99}Mo:^{99m}Tc generators were being produced using fission product material. In ten years the demand for stable ^{98}Mo had gone from nothing to a high figure and then back to nothing. The law of supply and demand, operating on such a short time scale, can be a very upsetting factor in an organization's planning.

Planning was to get harder yet. By the late 1960's, most research on nuclear medicine was dominated by the development of kits for use with ^{99m}Tc to provide scanning of human organs. Research on other radionuclides, all produced by neutron irradiation, had fallen off. Certain industrial firms were becoming convinced that new products for nuclear medicine would have to come from the use of accelerators, the oldest production technique. Cyclotrons had become available from industrial suppliers, and universities that had purchased cyclotrons were beginning to develop other radionuclide applications. Industrial organizations soon decided to follow suit, ordering cyclotrons and initiating research programs to find out how to make the new radionuclides.

Oak Ridge then faced a new problem. Nearly all of the new radionuclides required enriched stable isotopes. In fact, they could be

made from a large number of stable isotopes, depending upon the purity required, the type of cyclotrons to be used, and the cost of the isotopes. A question rapidly arose: which stable isotopes would be the growth stocks of the future?

The production of radionuclides in accelerators requires major decisions. The selection of the target material and the process to be used involve complex questions of physics and chemistry. This complexity leads to regulatory questions that compound the complexity. While industrial organizations like certainty or stability, regulatory agencies almost demand it. The energy of the accelerator beam, the beam particle, the target design, the time required for processing, and the time required to distribute the radionuclide all affect the purity of the final product. When a radionuclide such as ^{123}I can be produced by at least eleven different reactions involving five different target isotopes, making a decision on which ones to choose becomes highly uncertain. The amount of time that goes into the development of a new product in nuclear medicine can be drastically increased by these complexities, and the task of obtaining regulation approval can be extended by one to two years.

During that period of time ORNL must watch its inventories of target materials while discussing the use of alternatives with the industrial producer. The difficulty of predicting the demand for possible target materials leads to major problems for the industrial organization, for ORNL, and for the users.

To demonstrate the problems, let's take a look at how ^{201}Tl developed. The target situation is not as complex as that for ^{123}I, with the preferred reaction being p,3n on ^{203}Tl. This results in impurities of ^{200}Tl and ^{202}Tl, the amounts depending upon the time after bombardment is finished. Several years of research and development on this radionuclide were needed to reach the point at which a request for approval of a new drug could be filed. The application for approval was finally granted in late 1976. The company that first developed ^{201}Tl estimated that their yearly requirement for the target material might be fifties of grams per year. Within one year, however, it had become obvious that the requirement would be hundreds of grams, and ORNL was out of stock.

Thus, both ORNL and the company were in trouble. ORNL was faced with the problem of making more material on machines designed to make grams of material, not hundreds of grams. Furthermore, it was going to have lots of ^{205}Tl for which there was no market. The company was in trouble because it was no longer sure what its requirements were going to be. When would the growth rate begin to taper off? When would other NDA's be approved? How could it assure a constant supply without committing itself to high inventory costs?

The solution was as follows. ORNL asked the company to issue a purchase order for several hundred grams of the target material at a price to be determined after the material was made. With this commitment in hand, ORNL began the run. I can assure you that this was the first purchase order of over a million dollars ever issued by that company with no price guarantee. Industrial organizations do not like that sort of uncertainty.

There was one silver lining on the cloud, however. Every new batch of ^{203}Tl makes it necessary to requalify the raw material as to impurity levels and the quality of the final product. By making one very large commitment, the company was able to work for a long time using only one batch, without the added expense of requalification.

To make this review more meaningful to those of you who do not know how industrial firms normally operate with their suppliers, let me elaborate some principles of purchasing.

1. Either the price of the product is guaranteed for the life of the contract, or some escalation index is agreed upon at the time the contract is signed -- for example, the cost-of-living index.

2. If you buy a million dollars' worth of a product, you expect to pay a lower unit price than if you buy ten thousand dollars' worth.

3. Even if no contract is involved, the purchaser expects price increases in terms of a few percent per year, with no single increase being very large. A two-fold price increase in a single year is considered to be a sign of poor management on the part of the supplier.

4. Supply commitments will be made for one to two years, and sometimes even longer, in return for commitments on price, volume, or specifications.

5. It is not considered good management to become dependent on one source of supply.

In particular, unique problems arise when the government is the supplier. Industry does not like to make commitments when what happens to the supplier is dependent upon congressional approval of agency budgets. Above all, industry likes to have the price of a product bear an understandable relationship to its costs. It expects these costs to be determined by accounting procedures like those used by business firms and does not understand the vagaries of costing that Congress and agency controllers dream up.

The above points lead me to attempt to define the issues that should be looked at in the workshops.

1. Boom-bust cycles. How do industry and the government set up communications systems to exchange information? ORNL's inability to plan its budgets for future years, the tendency of industry to buy in large quantities as ORNL's inventory level decreases to what is considered too low a point, and the pricing policies of DOE should all be considered.

2. Industrial organization normally consider their supply needs to be proprietary information. Government, on the other hand, faces increasing demands to open its records to public scrutiny. What can be done?

3. What can be done to improve the long-term plan? Are Calutrons the most efficient device for producing stable isotopes? Are they capable of meeting the demands of the next ten years without major overhaul and expense? Should industry be making plans to buy from alternative sources, including foreign governments? Should DOE be supporting separation techniques specifically designed to produce stable isotopes?

4. Is there a possibility that the Calutrons at ORNL may be taken

over by a publicly-owned corporation? Is it politically or economically or technically feasible?

In my opinion, the workshop has its work cut out for it for the next two days in finding solutions to problems that may exist for years to come. This workshop is an encouraging move. Congratulations to the originator of the idea.

APPENDIX 7

Biomedical Research Applications of Electromagnetically Separated Enriched Stable Isotopes

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Abstract

The current and projected annual requirements through 1985 for stable isotopes enriched by electromagnetic separation methods were reviewed for applications in various types of biomedical research: (1) medical radioisotope production, labeled compounds, and potential radiopharmaceuticals; (2) nutrition, food science, and pharmacology; (3) metallobiochemistry and environmental toxicology; (4) nuclear magnetic resonance, electron paramagnetic resonance, and Mössbauer spectroscopy in biochemical, biophysical, and biomedical research; and (5) miscellaneous advances in radioactive and non-radioactive tracer technology. Radioisotopes available from commercial sources or routinely used in clinical nuclear medicine were excluded. Priorities and summaries are based on statements in the references and from answers to a survey conducted in the fall of 1981. Current requirements for enriched stable isotopes in biomedical research are not being satisfied. Severe shortages exist for ^{26}Mg, ^{43}Ca, ^{70}Zn, ^{76}Se, ^{77}Se, ^{78}Se, ^{102}Pd, ^{111}Cd, ^{113}Cd, and ^{190}Os. Many interesting and potentially important investigations in biomedical research require small quantities of specific elements at high isotopic enrichments.

Introduction

The requirements for electromagnetically separated enriched stable isotopes (1-5) in biomedical research and application are expanding dramatically. Biomedical research includes:

1. Medical radioisotope production, labeled compounds, and potential radiopharmaceuticals--i.e., research and development leading to transfer from scientific investigations to "routine" applications within society;
2. Nutrition, food science, and pharmacology--i.e., use of stable isotopes for investigating human nutrition, metabolism, and physiology, especially among preterm infants, children, and adults during the reproductive years, three groups in which the use of radioisotopic tracers constitutes a legitimate ethical concern because of potential biohazards;
3. Metallobiochemistry and environmental toxicology--i.e., low-level, long-term exposure to trace metals;
4. Nuclear magnetic resonance, electron paramagnetic resonance, and Mössbauer spectroscopy in biochemical, biophysical, and biomedical research--i.e., investigations of metals, metalloenzymes, metal macromolecular dynamics, and the study of cellular processes depending upon them by means of nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and Mössbauer spectroscopy with isotopes having non-zero nuclear spin; and
5. Advances in radioactive and non-radioactive tracer technology--i.e., activable tracers, bioanalytical

standards, radioactive sources for bioanalytical instrumentation, and miscellaneous applications.

DeWitt (6) reviewed the proposed and established uses of enriched stable isotopes in the biomedical field as of 1979. This report documents the more recent scientific literature and provides tabular summaries which identify the electromagnetically separated enriched stable isotopes and radioisotopes derived from them which are now used in research as shown by a survey conducted by the author in the fall of 1981 (Appendix I). Requests for milligram quantities of a specific stable isotope, however, while useful in scheduling operations at an isotope separation facility, do not necessarily indicate the potential value of the isotope in advancing scientific research.

In 1982 the only reliable sources of stable isotopes will be Oak Ridge National Laboratory (ORNL) and the USSR, which sells stable isotopes through a few companies in North America and Europe. Certain enriched stable isotopes are occasionally available from Israel and West Germany.

I. Medical Radionuclides and Radiopharmaceuticals

The importance of enriched stable isotopes as targets for medical radioisotope production was recognized in 1975 by a special task force (7) of the Energy Research and Development Administration (ERDA), which concluded that support for nuclear medicine would facilitate:

> ...the continued availability of target materials for the production of radionuclides. These materials (enriched stable isotopes) are required in the commercial production of most of the radionuclides used today; the only major source other than the ERDA facilities is the Soviet Union. Continuity of such production is essential for the practice of clinical nuclear medicine and for biomedical and environmental research.

The most significant events which have continued to promote medical radioisotope research and development are coupled with advances in expertise, recent advances in accelerator technology which permit national, regional, and local radioisotope production, advances in detection devices used in investigative research and clinical nuclear medicine, and the concurrent evolution of labeled compounds designed as potential radiopharmaceuticals to study normal physiology and for use in diagnosis and treatment of human disease.

Table 1 summarizes the current and projected requirements for 47 enriched stable isotopes that are needed to produce radionuclides intended for research in nuclear medicine. Research in this area includes development of the radionuclide in sufficient production yield and radiochemical and chemical purity for direct use or incorporation into labeled compounds. The derived radioisotopes, the labeled compounds, and the potential radiopharmaceuticals are intended for:

1. The non-invasive *in vivo* determination of physiological functions in man;
2. Therapeutic procedures requiring either a sealed and encapsulated radiation source or specific labeled

compounds for delivery of radiation to treat a diseased portion of the body; or

3. Sealed isotopes for implantation in the body to serve as a source of energy to power artificial organs.

New investigations are focused on the development of radionuclides which decay with optimum nuclear characteristics and the incorporation of these radionuclides into carrier compounds designed with prerequisite biological characteristics to be used as radiopharmaceuticals.

Recently introduced methods, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), and conventional devices, such as the gamma camera and compact cyclotrons, are responsible for the growing demand for isotopically enriched target material in hospitals and clinics. The advent of tomographic devices which permit a quantitative representation of radioactivity within a given volume element of the body and the ability to quantitate tracer studies for the evaluation of normal and pathological physiology is the focus of research in radiopharmaceutical chemistry and nuclear medicine (8-10).

Table 1 indicates the derived radionuclides having nuclear decay properties suitable for PET. PET studies require radionuclides which decay by emission of a high abundance of positrons, and usually the radionuclide has a half-life of less than 2 h. The popular short-lived radioisotopes for PET--^{11}C, ^{13}N, ^{15}O, ^{18}F, and ^{38}K--are not included, since they are not derived from electromagnetically separated enriched stable isotopes, nor are radioisotopes (e.g., ^{47}Ca, ^{67}Ga, ^{111}In, ^{201}Tl) which are routinely available from commercial sources for research with human subjects and routine clincial diagnosis. These radionuclides are more thoroughly discussed by Brantly (4) and Reba (5). Likewise, Table 1 does not list radionuclides and enriched isotopic targets required for the production of previously suggested radioisotopes, such as ^{43}K, ^{87m}Sr, ^{197}Hg, etc., which are not apparently being vigorously pursued for biomedical research or clinical applications. Background information on such radioisotopes is available elsewhere (6).

1. Influence of Isotopic Enrichment on Radionuclide Yield and Purity

Generally, the highest possible isotopic enrichment attainable is either preferred (to maximize production yields) or required (to eliminate or minimize radionuclidic impurities) in medical radioisotopes. The influence of isotopic enrichment of ^{124}Te on cyclotron production of high purity iodine-123 via the $^{124}Te(p,2n)^{123}I$ reaction offers a good example of this. Initial experiments and calculations in 1972 (11) predicted that the (p,2n) nuclear reaction on ultrahigh isotopic enrichment of ^{124}Te would result in ^{123}I of radionuclidic purity. The production yield could be surpassed only by the $^{127}I(p,5n)^{123}Xe \rightarrow ^{123}I$ production route. The generator route results in ^{123}I whose only radiocontaminant is <0.2 percent ^{125}I (13). Unfortunately, the (p,5n) reaction requires a projectile energy of ~60-50 MeV, which is beyond the capabilities of conventional compact medical cyclotrons (13). It is desirable to reduce the presence of ^{124}I($T_{1/2}$ = 4.16 d, γ's), since the longer-lived radionuclide increases the radiation burden to the patient, deteriorates the

TABLE 1. ENRICHED STABLE ISOTOPES AND RADIOISOTOPES DERIVED FROM THEM AND USED IN RADIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT.

Stable Isotope	ORNL Sales Inventory (g)	Projected Requirements (g/y)	Derived Radioisotope	Nuclear Reaction	Suitable for PET	Research applications
^{24}Mg	1	0.5	$^{26}Si \rightarrow ^{26m}Al$	$^{3}He,n$		metabolic tracer
^{26}Mg	0	0.1	^{28}Mg	t,p		metabolic tracer
^{50}Cr	10^{+}	1	^{51}Cr ^{51}Mn	n,γ d,n	X	labeled erythrocytes myocardial studies
^{52}Cr	8.5	4	^{51}Mn ^{52m}Mn	p,2n p,n	X	myocardial studies
^{57}Fe	18.5	4				radiopharmaceutical research
^{58}Ni	171	2	Cu isotopes		X	Cu metabolism, Wilson's Disease, Kinky Hair Disease, liver imaging
^{60}Ni	21	1				radiopharmaceutical research
^{63}Cu	14.5	0.2	^{64}Cu	n,γ	X	liver metabolism, calibration of biomedical instrumentation
^{66}Zn	6.3	0.2	$^{68}Ge \rightarrow ^{68}Ga$	α,2n	X	^{68}Ga generator, tumor localization, inflammatory sites blood flow, calibration of biomedical instrumentation
^{68}Zn	85	12	^{67}Ga	p,2n		
^{69}Ga	3.2	1	$^{68}Ge \rightarrow ^{68}Ga$	p,2n	X	radiopharmaceutical research
^{70}Ge	0.1	0.4	^{73}Se	α, n	X	analogs of amino acids and fatty acids
^{72}Ge	0.3	2	^{73}Se	^{3}He,2n	X	analogs of amino acids and fatty acids
^{74}Se	2.5	2	$^{75}Kr \rightarrow ^{75}Br$	^{3}He,2n	X	radiopharmaceutical research, e.g. fatty acids, steriods, receptor site affinity and displacement
^{76}Se	3.5	20	^{75}Br	p,2n	X	

(continued)

TABLE 1. ENRICHED STABLE ISOTOPES AND RADIOISOTOPES DERIVED FROM THEM AND USED IN RADIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT (continued).

Stable Isotope	ORNL Sales Inventory (g)	Projected Requirements (g/y)	Derived Radioisotope	Nuclear Reaction	Suitable for PET	Research applications
^{77}Se	0.17	20	^{77}Br	p,n		radiopharmaceutical research
			^{77}Br	p,2n		
			$^{77}Kr \rightarrow {}^{77}Br$	^{3}He,3n		generator of high purity ^{77}Br, excitation labeling
^{78}Se	1	10	^{77}Kr	^{3}He,3n		cerebral blood flow
^{80}Se	1.4	1				
^{79}Br	0.5	35	^{77}Kr	p,3n	X	cerebral blood flow
			$^{77}Kr \rightarrow {}^{77}Br$			generator of high purity ^{77}Br, excitation labeling
^{81}Br	0.5	20	^{77}Kr	p,5n	X	cerebral blood flow
			$^{77}Kr \rightarrow {}^{77}Br$			generator of high purity ^{77}Br, excitation labeling
^{96}Ru	0	0.2	^{97}Ru	n,γ		
^{92}Mo	10	5	^{92}Tc	p,n		analogs of ^{99m}Tc radiopharmaceuticals
^{95}Mo	4	1	^{97}Ru	α,2n		labeled monoclonal antibodies, hepatobillary agents
^{96}Mo	16	1	^{97}Ru	α,n		medical radioisotope research
^{100}Mo	1.5	2	^{99m}Tc	p,2n		alternate source of ^{99m}Tc other than generator
^{102}Pd	0	0.5*	^{103}Pd	n,γ		treatment of prostate cancer
^{108}Pd	0	0.1	^{109}Pd	n,γ		selective lymphatic ablation (therapy)
^{108}Cd	0.5	0.1				medical radioisotope research
^{112}Cd	0.2	0.1				medical radioisotope research
^{112}Sn	9.5		$^{113}Sn \rightarrow {}^{113m}In$	n,γ		radiopharmaceutical research

(continued)

TABLE 1. ENRICHED STABLE ISOTOPES AND RADIOISOTOPES DERIVED FROM THEM AND USED IN RADIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT (continued).

Stable Isotope	ORNL Sales Inventory (g)	Projected Requirements (g/y)	Derived Radioisotope	Nuclear Reaction	Suitable for PET	Research applications
^{116}Sn	6	1	^{117m}Sn	n,γ		tumor localization, cell labeling, therapeutic uses
^{121}Sb	0.5	25	^{121}I ^{119}Sb	α,4n	X	radiopharmaceutical research
^{123}Sb	0.5	20	^{119}Sb			
^{122}Te	22+	5-20	^{121}I ^{123m}Te	p,n n,γ	X	radiopharmaceutical research, e.g. analogs of fatty acids for myocardial studies, amphetamines for brain studies, iodohippuran for renal studies, labeled monoclonal antibodies calibration of biomedical instrumentation
^{123}Te	2.5+	25-50	^{123}I	p,n		radiopharmaceutical research
^{124}Te	15+	50	^{123}I	p,2n		ultrahigh isotopic enrichment required to minimize $^{124}I(T_{1/2}=4.2d)$ radiocontaminant
^{144}Sm	0	1	^{145}Sm	n,γ		ophthalmologic oncology
^{152}Gd	0.2	0.05	^{153}Gd	n,γ		biomedical instrumentation
^{164}Dy	6	0.5	^{165}Dy	n,γ		radiation synovectomy
^{168}Yb	0	0.5	^{169}Yb	n,γ		cisternography, labeled microspheres
^{185}Re	0.2	2	$^{188}Re \rightarrow ^{188}W$	n,γ		radiation synovectomy
^{187}Re	0.3	2	$^{188}Re \rightarrow ^{188}W$	n,γ + n,γ		radiation synovectomy
^{190}Os	0	100-200	$^{190}Os \rightarrow ^{191m}Ir$	n,γ		angiography, first-pass myocardial blood flow renal and cerebral perfusion, very significant potential
^{194}Pt	0	1.5	^{195m}Pt	n,γ		labeled antitumor agents
^{198}Pt	0.1	30				medical radioisotope research

(continued)

TABLE 1. ENRICHED STABLE ISOTOPES AND RADIOISOTOPES DERIVED FROM THEM AND USED IN RADIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT (continued).

Stable Isotope	ORNL Sales Inventory (g)	Projected Requirements (g/y)	Derived Radioisotope	Nuclear Reaction	Suitable for PET	Research Applications
^{202}Hg	2.9	6	^{201}Tl			alternate route of ^{201}Tl production for myocardial studies
^{203}Tl	+	+	$^{201}Pb \rightarrow ^{201}Tl$	p,3n		

+ ORNL separation in progress
Sales Inventory as of December 18, 1981

* Stated requirements (reference 43) of
20 g in 1984 and 100 g in 1986

high quality images that are otherwise attainable with ^{123}I, and reduces the effective shelf-life of the ^{123}I (14,15). High purity ^{123}I is nearly an ideal medical radioisotope because of its 13.3 h half-life and its emission of a high abundance of 159 keV photons.

A request (16) was made to ORNL for a special run to process a batch of previously enriched (>75 percent) ^{124}Te to achieve the highest isotopic enrichment of ^{124}Te attainable with the ORNL Calutrons. The natural isotopic composition of ^{124}Te is 4.61 percent. The ^{124}Te was isotopically enriched to 99.87 percent. Figures 1 and 2 illustrate the excitation functions (17) for the $^{124}Te(p,2n)^{123}I$ and $^{124}Te(p,n)^{124}I$ nuclear reactions on ^{124}Te isotopically enriched to 91.86 percent and 99.87 percent, respectively. In general, the excitation functions exhibit the expected trends for (p,n) and (p,2n) reactions on nuclides of intermediate mass. However, certain details require elaboration. The $^{124}Te(p,2n)^{123}I$ nuclear reaction has a flat maximum cross section of about 1 barn (1 barn = 10^{-24} cm^2) in the range of 23.5-25.5 MeV. The $^{124}Te(p,n)^{124}I$ nuclear reaction has a maximum cross section of about 450 millibarns at about 14.5 MeV. It is important to note the differences in the shapes of the excitation functions with the two different isotopic enrichments. The appearance of structure in the excitation functions at incident proton energies greater than 18 MeV is more evident with 91.86 percent enrichment ^{124}Te. The total cross section leading to ^{123}I via the $^{123}Te(p,n)^{123}I$ reaction is estimated as <1 percent for either enrichment of ^{124}Te. However, the 91.86 percent ^{124}Te contains 3.17 percent ^{125}Te. The $^{125}Te(p,3n)^{123}I$ and $^{125}Te(p,2n)^{124}I$ reactions are likely to be making an appreciable contribution to the yield of ^{123}I at Ep > 25 MeV, and the yield of ^{124}I at Ep < 16.5 MeV. The salient point is that the total cross section for formation of ^{124}I is substantially reduced by a factor of ~2 in the optimum section of the excitation functions of ultrahigh isotopic enrichment ^{124}Te.

Figure 3 summarizes the optimum conditions for the production of ^{123}I via the $^{124}Te(p,2n)^{123}I$ reaction with ^{124}Te of 99.87 percent and 91.86 percent enrichment. The percentage of ^{124}I relative to ^{123}I at the end of a short bombardment is given to the left for various incident proton energies. The right side of Fig. 3 depicts a time scale which can be used to read the level of ^{124}I which arises as a function of time. It is clearly evident that by using ultrahigh enrichment ^{124}Te the radionuclidic purity at the end of production is enhanced by a factor of 2. The upper level on the percentage of ^{124}I that is acceptable in a ^{123}I radiopharmaceutical depends somewhat on the intended use (12, 14,15,18). A study using isotopic enrichments of ^{124}Te of 99.87 percent, 96.21 percent, and 91.86 percent isotopic enrichments gave corresponding levels of ^{124}I at the time of production of 0.63 percent, 0.8 percent, and 1.08 percent, respectively. It was concluded that the ^{123}I produced with 99.87 percent ^{124}Te would have a shelf-life of >40 to ~53 h (18).

A number of effective radiochemical procedures have been developed for the quantitative recovery of the expensive and highly enriched target material (19-23).

Recent excitation function measurements of the $^{123}Te(p,n)^{123}I$

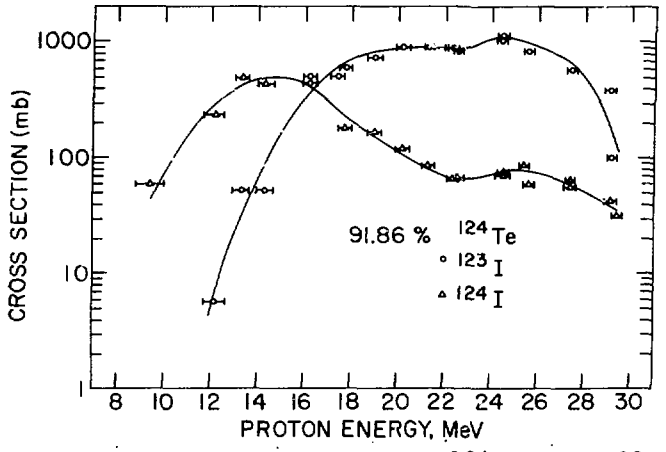

Fig. 1. Excitation Function for the $^{124}Te(p,2n)^{123}I$ and $^{124}Te(p,n)^{124}I$ Nuclear Reactions on a ^{124}Te Target of 91.86% Isotopic Enrichment. (Reference 17.)

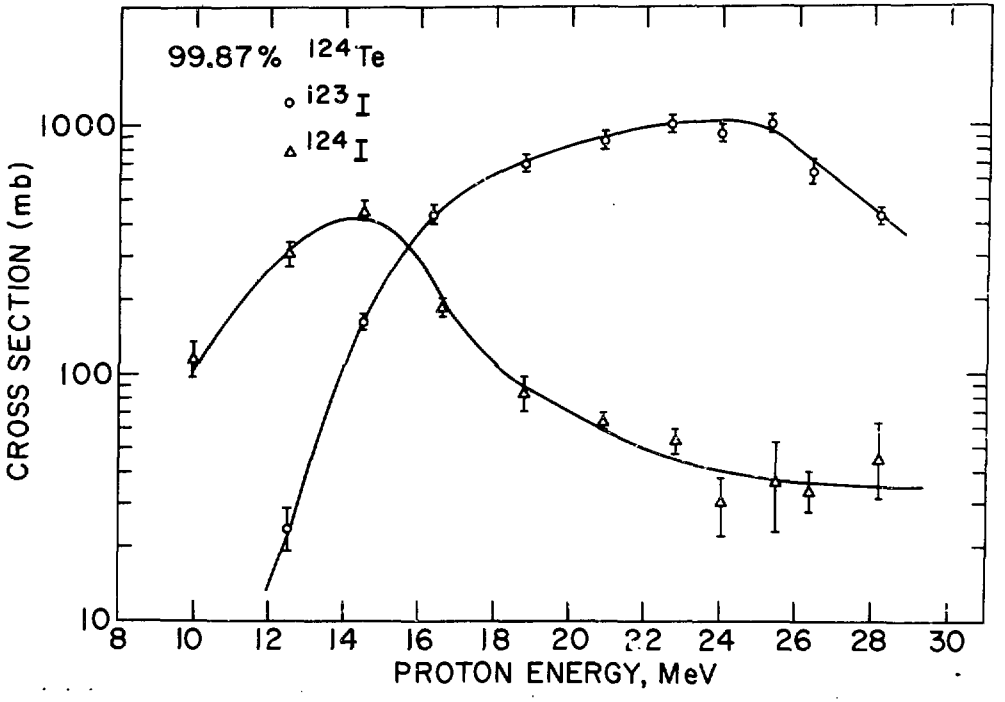

Fig. 2. Excitation Function for the $^{124}Te(p,2n)^{123}I$ and $^{124}Te(p,n)^{124}I$ Nuclear Reactions on a ^{124}Te Target of 99.87% Isotopic Enrichment. (Reference 17.)

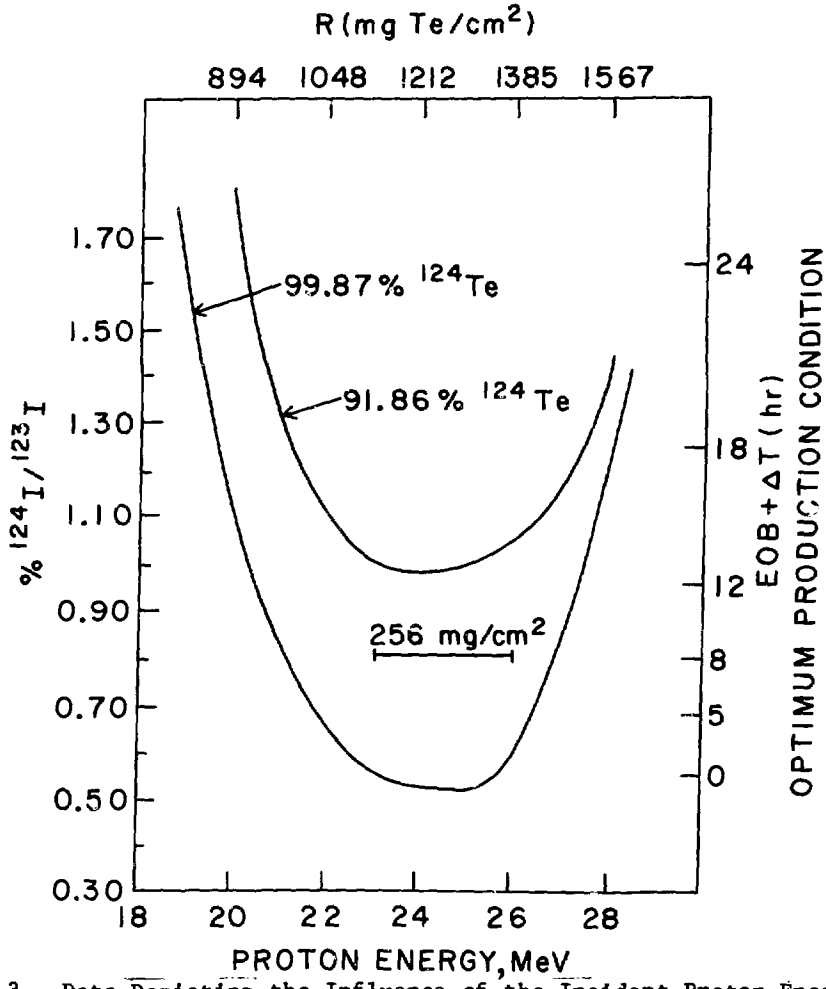

Fig. 3. Data Depicting the Influence of the Incident Proton Energy, Isotopic Enrichment of the ^{124}Te Target Material, Target Thickness and Time on the Radioisotopic Purity of ^{123}I Produced by the $^{124}Te(p,2n)^{123}I$ Nuclear Reaction. (Reference 17.)

nuclear reaction on 89.39 percent ^{123}Te have confirmed (24) production studies and extrapolations (25) that ^{123}Te containing 1.59 percent ^{124}Te as an isotopic impurity results in ^{123}I having a ^{124}I contamination of <0.4 percent at the end of the irradiation. The $^{123}Te(p,n)^{123}I$ reaction has an acceptable cross section at proton energies of less than 14 MeV and is therefore within the production capabilities of a compact hospital cyclotron. The radionuclidic purity is higher than that obtained with ultrahigh enrichment ^{124}Te and the $^{124}Te(p,2n)^{123}I$ route under optimum production conditions. A recent development (25) in ^{123}Te targetry provides a means of producing Curie quantities of high purity

^{123}I.

The author projects that the requirements for >88 percent isotopic enrichment ^{123}Te will exceed those presently noted for highly enriched ^{124}Te.

The presence of ^{124}I in ^{123}I results in increasing the radiation burden to the patient, regardless of what level of ^{124}I is considered acceptable for imaging purposes. Consideration can be given to a regulatory requirement for the use of ultrahigh isotopic Te target material if the application of the ^{123}I is for human use, and if ^{123}I produced by the $^{123}Xe \rightarrow {}^{123}I$ generator is not available.

2. Requirement of Enriched Isotopes for Development of Medical Radionuclides

The radioisotopes derived from enriched stable isotopes listed in Table 1 were identified as a focus of current research, either for the development of a radioisotope for evaluation either directly or for incorporation into labeled compounds. The labeled compounds are used in research principally to determine their potential applications in nuclear medicine. For example, highly enriched samarium-144 (3.1 percent natural isotopic abundance) is not presently available from ORNL. Researchers require this stable isotope in order to produce ^{145}Sm ($T_{1/2}$ = 340 d, γ = 0.0613 MeV) for evaluation as a sealed source of radiation *treatment for certain types of ocular tumors, such as melanoma.* Alternate (but unevaluated) routes for the production of no-carrier-added ^{145}Sm also require targets of high isotopic enrichment, e.g., the $^{143}Nd(^{3}He,n)^{145}Sm$, $^{143}Nd(\alpha,2n)^{145}Sm$, $^{144}Nd(\alpha,3n)^{145}Sm$, $^{144}Nd(^{3}He,2n)^{145}Sm$, and $^{142}Nd(\alpha,n)^{145}Sm$ nuclear reactions.

Several of the desired radionuclides can be produced by more than one nuclear reaction on one or more isotopically enriched targets. For example, the desirable features of selenium-73 as a possible replacement of ^{75}Se ($T_{1/2}$ = 120.4 d) are evident by its physical characteristics ($T_{1/2}$ = 7.2 h) and nuclear decay properties, which are suitable for detection on a gamma camera (γ = 360 keV, 95.3 percent) or a PET (β^{+} = 1.29 MeV, 511 keV = 130 percent). There is interest in developing Se compounds as potential radiopharmaceuticals (26,27). Selenium responsive-deficiency diseases, dietary and ecological effects on human and animal health, and the role of the trace metal as the active site of gluthione peroxidase and other enzymes are areas in which ^{73}Se could be used as a radiotracer. (See Sections II and III.) The production of ^{73}Se by nuclear reactions on targets of natural isotopic composition results in the concurrent production of 0.2-0.5 percent ^{75}Se as a radionuclidic impurity (28-30). However, the $^{72}Ge(^{3}He,2n)^{73}Se$ nuclear reaction on ^{72}Ge isotopically enriched to 96.4 percent results in ^{73}Se with a radionuclidic purity of >99.99 percent (29). The $^{70}Ge(\alpha,n)^{73}Se$ nuclear reaction on >95 percent isotopic enrichment ^{70}Ge promises to be an alternate and acceptable route to high radionuclidic purity ^{73}Se (29).

Recent studies with 98.6 percent ^{202}Hg have led to the suggestion that the $^{202}Hg(p,2n)^{201}Tl$ nuclear reaction may eliminate the need for two-step processing of ^{201}Tl (31,32) required by the $^{203}Tl(p,3n)^{201}Pb$ ^{201}Tl production method and be within the production capabilities of

some hospital cyclotrons.

3. Requirements Based on Radioisotope Production Yield

Thallium-201 is an example of the successful development of a radioisotope from the research stage to commercial production for worldwide clinical application. This radiopharmaceutical is routinely used for the evaluation of myocardial disease (5). The $^{203}Tl(p,3n)^{201}Pb \rightarrow {}^{201}Tl$ production route was introduced (33) in 1972. Various laboratories have since optimized the cyclotron production of the $^{201}Pb \rightarrow {}^{201}Tl$ generator (32,34-38) and methods for the quantitative recovery of enriched target material (37,39). Industry adopted the use of isotopically enriched ^{203}Tl as target material based entirely on economic considerations. The natural abundance of ^{203}Tl is 29.5 percent, and therefore a higher production yield per unit irradiation time is obtained.

Seven isotopes of osmium occur in nature, with the natural abundance of ^{190}Os being 26.4 percent. The production of the $^{191}Os \rightarrow {}^{191m}Ir$ generator (40,41) via the $^{190}Os(n,\gamma)^{191}Os$ reaction is limited by the cross section for neutron capture, the neutron flux of the nuclear reactor, and to a lesser degree by radiochemical factors. Nuclear reactions on the natural occurence of Os do not produce radioactivities which interfere with the generator eluent (^{191m}Ir).

4. Identification of Severe Shortages of Electromagnetically Separated Isotopes

ORNL has the capability to enrich 224 stable isotopes by electromagnetic separation techniques. Unfortunately, the ORNL sales inventory currently lacks about 25 percent (i.e., 65) of the enriched isotopes. The isotopic enrichment of the materials available from the ORNL sales inventory do not always meet current research requirements. Past experience indicates that ultrahigh enrichment of certain stable isotopes (e.g., ^{124}Te) is not available on request. However, ORNL has been responsive to special requests for specific enriched isotopes.

Medical radioisotope research and development activities utilizing cyclotrons, accelerators, and reactors often require small (10-50 milligram) quantities of several isotopes in order to evaluate optimum production routes. Therefore, target material with the prerequisite isotopic enrichment is required in order to introduce new radioisotopes into medical applications. Table 2 summarizes four examples from the recent literature in which small quantities of enriched isotopes were utilized to evaluate nuclear reactions and irradiation conditions, or to develop radiochemical separation schemes, in order to promote a medical application.

Research with the osmium-191 → iridium-191m generator (40-42) has progressed with difficulty, due to the unavailability of isotopically enriched ^{190}Os. The parent, ^{191}Os, has a half-life of 15.4 d. The ^{191m}Ir daughter decays with a half-life of 4.96 s by emission of 65 keV and 129 keV photons in 58 percent and 30 percent abundance, respectively. The $^{191}Os \rightarrow {}^{191m}Ir$ generator can deliver multiple doses of ^{191m}Ir for first-pass angiography, i.e., the detection and quantitation of shunts and the evaluation of cardiac function. Treves et al. (41,42) have shown that the low radiation dose, high information density, and

TABLE 2. EXAMPLES OF RECENT PAST REQUIREMENTS FOR < 50 mg QUANTITIES OF ENRICHED STABLE ISOTOPES IN ORDER TO EVALUATE THE EFFECTIVE PRODUCTION ROUTE, TARGET MATERIAL AND ISOTOPIC ENRICHMENT FOR "NEW" MEDICAL RADIOISOTOPES.

Radionuclide	Isotopic Enrichment	Nuclear Reactions	Reference
^{28}Mg		$^{26}Mg(t,p)$	47
		$^{26}Mg(\alpha,2p)$	48
		$^{27}Al(\alpha,3p)$	48
		$^{27}Al(t,2p)$	47
		$^{30}Si(\gamma,2n)$	49
^{30}P		$^{27}Al(\alpha,n)$	50
		$^{28}Si(^{3}He,p)$	51
		$^{28}Si(\alpha,d)$	51
		$^{31}P(p,pn)$	50
		$^{32}S(d,\alpha)$	51
^{51}Mn		$^{50}Cr(d,n)$	52,181
		$^{52}Cr(p,2n)$	52
		$^{51}V(^{3}He,3n)$	
^{123}I		$^{120}Te(^{4}He,n)^{123}Xe$-$^{123}I$	11
		$^{122}Te(^{3}He,2n)^{123}Xe$-$^{123}I$	53
		$^{122}Te(^{4}He,3n)^{123}Xe$-$^{123}I$	53,54
		$^{122}Te(d,n)^{123}I$	53
		$^{122}Te(^{4}He,p2n)^{123}I$	53
		$^{122}Te(^{3}He,pn)^{123}I$	53
		$^{123}Te(^{3}He,p2n)^{123}I$	53,55
		$^{123}Te(^{3}He,3n)^{123}Xe$-$^{123}I$	53,55
	79.2%	$^{123}Te(p,n)^{123}I$	21
	77%	$^{123}Te(p,n)^{123}I$	28
	87.45%	$^{123}Te(p,n)^{123}I$	25
	88%	$^{123}Te(p,n)^{123}I$	24
	91.86%	$^{124}Te(p,2n)^{123}I$	17
	99.87%	$^{124}Te(p,2n)^{123}I$	17
		$^{124}Te(^{3}He,4n)^{123}Xe$-$^{123}I$	55
		$^{124}Te(^{3}He,p2n)^{123}I$	55
		$^{125}Te(p,3n)^{123}I$	11
		$^{121}Sb(^{4}He,2n)$	53
		$^{121}Sb(^{3}He,n)$	53
		$^{123}Sb(^{3}He,3n)$	11

ability to perform serial studies with ^{191m}Ir every 30 s indicates that the $^{190}Os \rightarrow {}^{191m}Ir$ generator can be transferred from research to clinical determinations in children and adults. Other potential research applications include: (1) measurement of ventricular volumes; (2) detection of left-to-right and right-to-left shunts; (3) evaluation of renal perfusion; (4) evaluation of pulmonary arterial perfusion; (5) venography, diagnosis of superior or inferior vena caval obstruction, or evaluation of other venous drainage; (6) evaluation of blood flow to tumors by selective arterial infusion; and (7) evaluation of cerebral perfusion. An annual requirement for 100-200 grams of 95 percent isotopic enrichment of ^{190}Os is projected for the immediate future.

There is a need for highly enriched ^{102}Pd (1.0 percent natural abundance), which has been absent from the ORNL sales inventory since fiscal 1980. One investigator (43) concerned with the research and commercial development of an agent for the treatment of prostate cancer cited a purchase order for 20 grams of ^{102}Pd in 1984 and another 100 grams in 1986. Lesser quantities of enriched ^{108}Pd are needed for research on selective lymphatic oblation via ^{109}Pd therapeutic agents (44,45). Enriched ^{185}Re and/or ^{187}Re are needed for a project in radiation synovectomy at Harvard Medical School (46).

Recent interest in high purity ^{77}Kr for neurophysiological research and PET determination of cerebral blood flow (52,56,57) or regional lung function has stimulated a demand (57) for enriched ^{76}Se and ^{77}Se for the cyclotron production of the radioisotope. Enriched selenium isotopes are also utilized in the production of radiopharmaceutical quality ^{77}Br (52,57-64). Isotopically enriched ^{74}Se and ^{76}Se have been proposed as targets for obtaining ^{75}Br (65,66).

Highly (>87 percent) enriched ^{123}Te and ultrahigh (>99 percent) enrichment ^{124}Te for the cyclotron production of ^{123}I via the $^{123}Te(p,n)^{123}I$ and $^{124}Te(p,2n)^{123}I$ reactions, respectively, is also required.

Continued emphasis on medical radioisotope research and unexpected developments in the availability of a new medical radioisotope, or a breakthrough in the preparation of unique radiopharmaceuticals for the user-community, make it very difficult to project accurately the quantities of electromagnetically separated stable isotopes that will be required for medical applications in 1990. An estimate of the projected annual requirements for medical radionuclide and radiopharmaceutical research through 1985 is noted in Table 1. The estimates are probably conservative, since the radiopharmaceutical and nuclear medicine fields are expected to continue to expand.

Table 3 is illustrative of the trends in ORNL's total sales of four enriched stable isotopes irrespective of isotopic enrichment or intended use. The minor requirements for ^{124}Te and ^{203}Tl for research and development of ^{123}I and ^{201}Tl, respectively, in the early 1970's was followed by an increase in sales by a factor of >100 and >1,000 in 1981, respectively. By contrast, research with small quantities of ^{102}Pd and ^{190}Os has depleted the sales inventory of both stable isotopes. Further research and rapid development to enable the widespread use of the $^{191}Os \rightarrow {}^{191m}Ir$ generator by the medical community seems to be halted.

TABLE 3. EXAMPLES OF TRENDS IN THE ORNL SALES OF ELECTROMAGNETICALLY SEPARATED STABLE ISOTOPES (COMBINED ENRICHMENTS) THAT DEVELOPED FROM RESEARCH INVESTIGATIONS OF ALL TYPES TO COMMERCIAL MEDICAL APPLICATIONS (^{203}Tl, ^{124}Te) AND OF ^{102}Pd AND ^{190}Os WHICH ARE PROJECTED TO EVOLVE FROM PRESENT RESEARCH REQUIREMENTS TO A COMMERCIAL DEMAND.

	Milligrams sold (all enrichments) per fiscal year			
Fiscal Year	^{102}Pd	^{124}Te	^{190}Os	^{203}Tl
1970	588	589	0	1670
1971	935	2876	0	739
1972	3575	2896	0	1365
1973	100	9711	100	16790
1974	43	20170	70	3902
1975	45	3510	0	143487
1976	163	22735	24	219813
1977	17	16541	2560	252310
1978	292	16785	1555	193319
1979	130	41700	1250	464600
1980	0	19675	550	707637
1981	0	38682	175	1242843
ORNL Stock (mg) As of 12/18/81	0	15,000 + Processing	0	Processing

5. Current Research Efforts with Compounds Labeled With Radioisotopes Derived From Targets of Electromagnetically Separated Isotopes.

Table 4 is provided to add detail to selected examples of biomedical applications of the radioisotopes listed in Table 1. All examples are from the current literature and represent research efforts to synthesize or evaluate various types of substrates as radiotracers (potential radiopharmaceuticals) of specific pathological states or physiological processes. The subject areas of most intense research are the study of brain and heart blood flow and metabolism, CNS processes (including receptor bending and cisternography), and tumor localization. The most popular derived radioisotopes for research during 1980-1981 were ^{123}I, ^{75}Br, ^{77}Br, ^{97}Ru, and $^{190}Os \rightarrow ^{191m}Ir$. Animal studies with ^{131}I-iodobenzylguanidine (177); 4-^{124}I-iodophenyltrimethylammonium ion, an iodinated acetylcholinestrase inhibitor (178); ^{131}I-iodomethyltrimethyl ammonium chloride (179); and two ^{125}I-iodobenzoyl derivatives of acebutolol (180), suggest that the labeled compounds would be potential myocardial imaging agents if the radioactive label were switched to ^{123}I. Research with ^{47}Ca, ^{67}Ga, ^{111}In, and ^{201}Tl is usually human subject or clinically oriented and (with the exception of ^{111}In for labeling blood components) is not cited in Tables 1 or 4. See Reba (4).

II. Nutrition, Food Science, and Pharmacology

Biochemists, nutritionists, and pharmacologists have recognized the complementary features and additional resources of double and triple label tracer technology. Multiple isotopic label techniques with ^{2}H, ^{13}C, ^{15}N, ^{32}S, ^{34}S, ^{35}Cl, ^{37}Cl, ^{79}Br, and ^{81}Br (the first three are not electromagnetically separated isotopes) are used extensively in pharmacological studies to investigate lipid, carbohydrate amino acid, and drug metabolism (102). Labeling with stable and radioactive isotopes is one of the most convenient methods for the simultaneous estimation of pharmacokinetics (radioisotopes) and structure elucidation (mass spectrometry) in studies of drug metabolism (103).

The accuracy of radioactive measurements exceeds that of conventional analytical measurements. Most investigations in nutrition and food science (104-108) utilize commercially available longer-lived radioisotopes derived from electromagnetically separated enriched isotopes (^{45}Ca, ^{47}Ca, ^{55}Fe, ^{59}Fe, ^{65}Zn, ^{75}Se, etc.). These long-term metabolic studies preclude the use of short-lived accelerator-produced radioisotopes. The absorbed radiation dose resulting from the use of long-lived radioisotopes cannot be justified in other than elderly or very sick subjects (105,109,110). Ethical concerns therefor preclude administration of radioactive substrates to preterm infants, children, pregnant, lactating, or menstruating women, and adults in their reproductive years if no known benefit to the subject will arise from the research.

Hence, the utilization of radioisotopes in human nutrition research is limited. Ethical concerns and biomedical hazards present potentially serious shortcomings (109). Young (109) has strongly advocated the stable isotope tracer technique as the only potentially applicable,

TABLE 4. EXAMPLES OF RADIOTRACERS BEING INVESTIGATED AS POTENTIAL RADIOPHARMACEUTICALS LABELED WITH RADIOISOTOPES DERIVED FROM ENRICHED STABLE ISOTOPES

Analog Classification	Radioisotope	Radiotracer	Area of Research and Potential Applications	Selected Reference
Fatty Acids	^{123}I	17-iodohepadecanoic acid	Evaluation of heart disease	67-69
	^{123}I	ω-(-p-iodophenyl)-pentadecanoic acid	metabolism, metabolic trapping	69, 70-72
	$^{82}Br, ^{77}Br, ^{75}Br$	ω-(-p-bromophenyl)-pentadecanoic acid		72,74
	$^{123}I, ^{77}Br, ^{75}Br$	Various fatty acid analogs		67,74-79
	^{123m}Te	9-telluraheptadecanoic acid and tellura-fatty acid analogs		80,81
	$^{75}Se, ^{73}Se$	Selena-fatty acid analogs		82
Guanethidine	^{123}I	Meta-iodobenzylguanidine	adrenomedullary imaging agent noradrenaline storage analog	83 166
Steroids	$^{82}Br, ^{123}I$	α-halostilbenes related to diethylstilestrol	uterus and mammary tumors	84
	^{77}Br	16 α-bromoestradiol-17β		85
	^{77}Br	2-and 4-bromo isomers of estradiol and 17 α-ethynylestradiol	receptor binding	86
	^{117m}Sn	23-(trimethylstanna)-24-nor-5α-cholan-3β-ol	adrenal imaging	
	^{123m}Te	23-(isopropyltelluro)-24-nor-5α-cholan-3β-ol		166
Amines	^{123}I	Analogs of 4,6-diiodo-salicylaldehyde	brain imaging	87,88
	^{123}I	40 analogs of iodophenylalkyl amines	brain localization	167
	^{123}I	N-isopropyl-para-iodoamphetamine		168
	$^{75}Se, ^{73}Se$	di-β(morpholinoethyl)-selenide di-β(piperidinoethyl)-selenide		27 27

(continued)

TABLE 4. EXAMPLES OF RADIOTRACERS BEING INVESTIGATED AS POTENTIAL RADIOPHARMACEUTICALS LABELED WITH RADIOISOTOPES DERIVED FROM ENRICHED STABLE ISOTOPES

(continued)

Analog Classification	Radioisotope	Radiotracer	Area of Research and Potential Applications	Selected Reference
Barbiturates	$^{75}Se, ^{123m}Te$	Analogs of 5-alkyl-5-(ω-bromoalkyl) diethylmalonate	brain imaging agents	89
CNS active drugs	$^{77}Br, ^{75}Br$	p-bromosporoperidol	dopamine receptor binding	90,91
	^{123}I	4-iodo-2,5-dimethoxyphenylisopropylamine	psychotomimetic agent	92
	^{123}I	analog of benperidol	dopamine receptor studies	93
Amino acids	^{123}I	L-3-iodo-α-methyltyrosine	pancreas imaging	94
	^{75}Br	L-3-bromo-α-methyltyrosine		94
	^{73}Se	benzoselenoamines and amino acids		26,164,165
Trizines	^{123}I	condition/variation study for labeling pyrrolidyl triazenes	synthetic intermediate to radiopharmaceuticals	95
Proteins	^{77}Br	human serum albumin, fibrinogen	model compounds	169
Rare gas	^{77}Kr	gas for inhalation	cerebral blood flow lung function	52,64
Inorganics and Complexes	$^{191}Os \rightarrow ^{191m}Ir$	^{191m}Ir	first-pass angiography, etc.	40
	$^{97}Ru, ^{123}I, ^{203}Pb$	labeled monoclonal antibodies	tumor localization	
	^{97}Ru	Ru-Red, Ru-heparin Ru-chondroitin sulfate	tumor localization	182

(continued)

TABLE 4. EXAMPLES OF RADIOTRACERS BEING INVESTIGATED AS POTENTIAL RADIOPHARMACEUTICALS LABELED WITH RADIOISOTOPES DERIVED FROM ENRICHED STABLE ISOTOPES

(continued)

Analog Classification	Radioisotope	Radiotracer	Area of Research and Potential Applications	Selected Reference
Inorganics and Complexes	^{97}Ru	Ru-PIPIDA (N,α-(p-isopropyl acetanilide)	Delayed studies of bilary tract	96
	^{97}Ru	Ru-transferrin	tumor localization	170
	^{97}Ru	Ru-DTPA (diethylenetriamine penta-acetic acid)	cisternography	97
	^{97}Ru	Ru-DMSA	delayed renal imaging	171
	^{55}Co	Co-DTPA	quantitative cisternography	98
	^{92}Tc	pertechnate	PET studies	99
	$^{97}Ru, ^{111}In$	metal oxime and other complexes	cellular blood elements	100
	$^{117m}Sn, ^{55}Co$	metal oxime and other complexes	platelets, red cells, etc.	101
	^{165}Dy	ferric hydroxide macroaggregates	radiation synovectomy	172
	$^{51}Mn, ^{52m}Mn$	manganous chloride	heart imaging	173,174
	^{52}Mn	EDTA, DTPA, CDTA	kidney function	175
	^{68}Ga	Ga-dihydroxyanthraquinones	liver and spleen RES	176

non-invasive, non-hazardous approach relevant to mineral bioavailability studies in man. [Bioavailability is the fraction of the dietary intake of the element that is absorbed by the body from the gastrointestinal tract.]

Animal models do not necessarily provide precise quantitative estimates of the actual availability of minerals in the total diet or dietary constituents of healthy humans under free-living conditions (111). Therefore, studies in man are essential. Current research (110-146) on human mineral metabolism, particularly tracer mineral metabolism, focuses on understanding nutritional requirements for, and the intermediate metabolism of, substances. Enriched stable isotope tracer methods are being used to study:

1. The effect of dietary factors--i.e., diet composition, food processing, and food fortification;
2. The influence of the chemical forms of the mineral on absorption;
3. The fraction of the mineral which is absorbed from the diet;
4. Kinetics of fecal excretion of dietary minerals;
5. The extent of endogenous excretion into the gastrointestinal tract; and
6. The role of dietary minerals in relation to degenerative disease.

New studies are considered important because of the changes that are occurring in the world's food supply. Nutrient density and caloric intake are gradually decreasing (107,111,125). Significant (i.e., gram) quantities of highly enriched Mg, Ca, Fe, Cu, Zn, and Se isotopes are required. The stable isotope technique for absorption studies requires that two or more stable isotopes occur in nature. One or more enriched stable isotopes of the same or different elements can be conveniently utilized in an experiment. For example, there are six stable isotopes of selenium available in enriched form from ORNL. Of the 28 elements thought to be of potential nutritional significance, 22 can be utilized with the stable isotope tracer technique. Those elements are Mg, Si, Ca, Ti, V, Cr, Fe, Ni, Cu, Zn, Se, Sr, Mo, Ag, Cd, Sn, Sb, Ba, W, Hg, and Pb. Micronutrients (or toxins) that will receive attention in the future include Cd, Bi, Os, Tl, and Pb. It is difficult to know which trace minerals are of the greatest importance at present because the field is so young.

Table 5 summarizes the current requirements for 31 isotopes. In 11 instances the projected annual requirements for nutrition-related research exceed the sales inventory at ORNL. Investigators have noted that because large quantities of non-recoverable enriched isotopes are required, the cost of the enriched isotope becomes a limiting factor for the experiment. The use of Ca isotopes has been severely restricted by high price (e.g., ^{46}Ca isotopically enriched to 43.35 percent costs $2,330.20/mg), and by the limited availability of suitable measurement facilities. NASA, for example, is concerned with changes in calcium metabolism observed in spaceflight (116,117) and makes frequent requests for multi-100 gram quantities of various enriched Ca isotopes. NASA

TABLE 5. STABLE ISOTOPES USED IN INVESTIGATIONS OF TRACER MINERAL METABOLISM, BIOCHEMISTRY AND NUTRITION SCIENCE.

Isotope	ORNL Sales Inventory* (g)	Projected Requirements (g/y)
^{25}Mg	1	4-8
^{26}Mg	0.1	5-10
^{40}Ca	21	100's
^{42}Ca	1	2
^{44}Ca	14	4.5
^{46}Ca	0.18	1
^{48}Ca	1	2
^{50}Cr	10	1
^{54}Cr	3	1
^{54}Fe	3	4-8
^{57}Fe	18.5	3-8
^{58}Fe	2	0.4-1.5
^{61}Ni	5	0.5
^{62}Ni	30	0.5
^{64}Ni	5	0.5
^{63}Cu	14.5	1
^{65}Cu	6	2.5
^{64}Zn	3.5	2.5
^{67}Zn	1	7-10
^{68}Zn	85	2-5
^{70}Zn	0+	1.5-3
^{74}Se	2.5	1.5
^{76}Se	3.5	2-10
^{77}Se	0.17	2-10
^{80}Se	1.4	0.2
^{95}Mo	4	0.6
^{96}Mo	16	0.6
^{100}Mo	1.5	1.0
^{100}Cd	0.5	0.2
^{108}Cd	0.5	0.2
^{116}Cd	3	0.5

* Sales Inventory as of December 18, 1981

research efforts center on devising countermeasures to long-term effects, such as fracture due to vertebral mineral loss and renal stones from high filtered calcium load. Such disorders would be severe problems if they occurred during space flights. The relative bone reabsorption and diet absorption of calcium is well established and can be measured directly with high precision. Current research efforts include the study of calcium metabolism in disuse osteoporosis in monkeys using continuous tracer (^{40}Ca, ^{48}Ca) and pulse tracer kinetics (^{47}Ca) (117), human nutritional and metabolic studies with ^{46}Ca and ^{48}Ca (118, 146), and studies of calcium metabolism in children with ^{40}Ca, ^{42}Ca, ^{43}Ca, ^{44}Ca, ^{46}Ca, and ^{48}Ca (119).

Intrinsically labeled foodstuffs are prepared for human feeding experiments to investigate the availability of such minerals as ^{65}Cu, ^{54}Fe, and ^{67}Zn from such foods as wheat, corn, and sunflower seeds. Enrichments as high as 86 atom percent excess ^{65}Cu have been obtained in harvested wheat after a single injection during pollination (127).

Schwartz et al. (114) prepared five leafy vegetables intrinsically labeled with ^{26}Mg and determined that the intrinsic tracer was nearly 100 percent exchangeable with extrinsic ^{28}Mg (a derived radioisotope) during the digestion and absorption processes in rats. Dual tracer technique studies (112,113) in man demonstrated that isotopically enriched ^{26}Mg expanded the scope of investigation of magnesium absorption in man beyond that possible only with ^{28}Mg ($T_{1/2}$ = 21.3 h).

Isotopically enriched isotopes have been utilized to study the effect of oral contraceptives (120) and on the bioavailability of Cu, Zn, and Fe (109,120,124,125,128,133,139-142) and the gastrointestinal absorption of Mg, Ca, Fe, Zn, Cu, and Se (112-114,118,120-123,130,135). Intrinsic labeling of poultry meat with ^{74}Se, ^{68}Zn, and ^{70}Zn demonstrated an effective method to prepare labeled animal foods for human consumption (139,142). The experimental process is depicted in Fig. 4. Feeding Se to chickens resulted in endogenous-labeled eggs which were fed to pregnant women to measure Se absorption (147). Young and coworkers (135,140) studied quantitative absorption, excretion, and retention of single and multiple oral doses of ^{74}Se-selenite in healthy adult male volunteers. Their work: (1) assessed the capabilities and limitations of enriched stable Se isotope methodology in metabolic studies in man; and (2) established the degree of isotopic enrichment possible in the biological matrices relevant to the study of Se metabolism.

The bioavailability of stable isotopes of trace elements is measured by means of neutron activation analysis, gas chromatography/mass spectrometry of volatile metal chelates, and thermal ionization mass spectrometry. Charged particle activation analysis has not yet been exploited. A significant need exists for further development of analytical methods for accurate and rapid measurement of isotopic abundance and ratios in biological media. (See Section V for a discussion on research with bioanalytical standards.) Neutron activation analysis is further advanced through mass spectrometry for routine analysis of Fe, Zn, Cr, and Se, but mass spectrometry is of broader scope (110). These analytical methods have been adapted to the analysis of blood, urine, and feces (110,115,118,126,127,129,132,134,136,137).

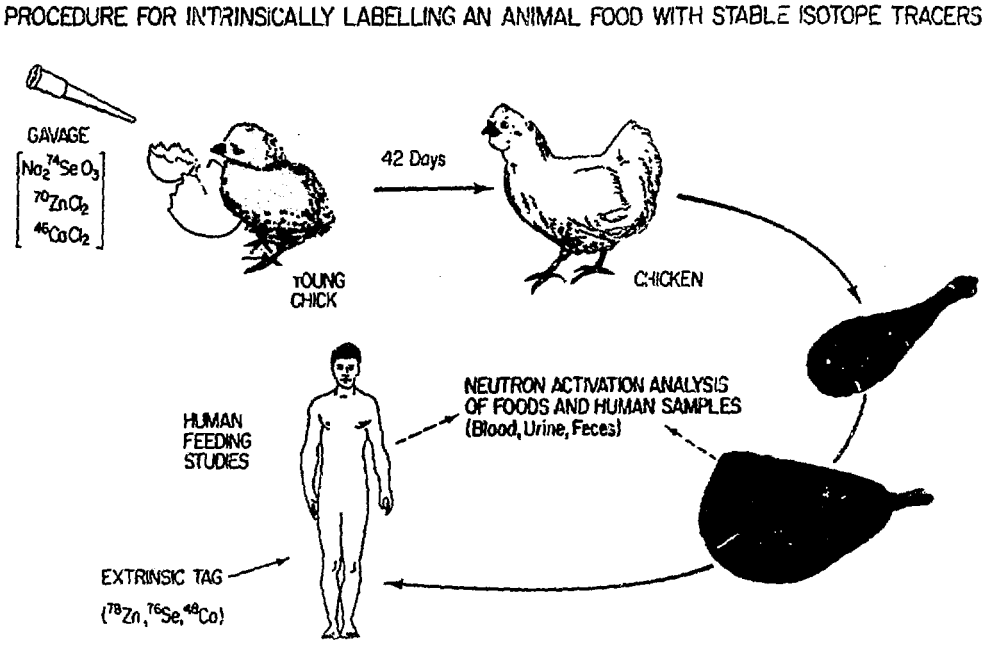

Fig. 4. A General Sketch Indicating the Use of the Chicken as an Animal Model of Intrinsically Labeled Food Source to Test Exchangeability of Intrinsic and Extrinsic Absorption Pools of Trace Minerals in Man. The Chicks are Gavaged with Enriched Isotopes During the Growth Period to Achieve Sufficient Enrichment of the Enriched Isotope in Edible Tissues Prior to Human Consumption. Trace Mineral Absoption Pools are Determined by Analysis of the Food and Human Samples. (From: Janghorbani and Young, reference 140).

III. Metallobiochemistry and Environmental Toxicology

Assessment of the physiological responses of long-term exposure to ingested metals is fundamental in establishing the toxicological effects of trace metals on human health (148). Quantitative prediction of toxicity is based on extrapolation of metallobiochemical results from long-term low-level exposure of laboratory animals. Due to severe

analytical considerations (i.e., assay in biological tissue at the subcellular and molecular levels), most metabolic and toxicological investigations have dealt with larger than normal doses. Hence, subtle environmental influences have not been directly determined. New and sensitive nuclear and radiochemical techniques (149-151), combined with production of high specific activity radioisotopes (and radiochemicals) with accurate quality controls of the final solutions used for biochemical purposes, have been introduced to trace low doses of metal pollutants. Recent investigations have demonstrated that many of the difficulties of extrapolation of animal data to human beings can be eliminated while providing insights into the biochemical mechanisms of trace metals.

Table 6 lists the production method and nuclear properties of 29 metallic radiotracers that have been prepared and subjected to analytical controls for metallobiochemical investigations of present environmental levels of heavy metals. Studies in progress or contemplated include interrelationships between iron and vanadium, chemobiokinetics, and cellular or binding components of chromium, arsenic, antimony, nickel, mercury, copper, lead, and selenium. Tracers of zinc, cadmium, silver, and tin can be utilized for metallothionein studies, while the determination of metabolic patterns is a focus with thallium, mercury, arsenic, lead, and antimony. Trace concentrations of several of the rare earths are easily measured.

Production of radiotracers with high radionuclidic purity and high specific activity requires the highest possible isotopic enrichment of target materials. For example, ^{72}As ($T_{1/2}$ = 26 h, β^+) can be produced in high radionuclidic purity via the (p,n) reaction on enriched ^{72}Ge or via the decay of ^{72}Se($T_{1/2}$ = 8.5 d) following the (α,2n) on isotopically enriched ^{70}Ge. Employing ^{74}Ge or ^{76}Ge enriched targets, the ^{74}As can be produced in high yield and radionuclidic purity via (p,n) or (p,2n) nuclear reactions, respectively. To the contrary, however, ^{71}As cannot be produced without radionuclidic contamination even if germanium enriched targets are used (152,153).

Contamination of the recovered radiotracer with non-radiotracer metallic impurities should be avoided. In order to meet the criteria of low-level exposure, it is desirable that most of the radiotracers be prepared at the no-carrier-added level. Even then, a "carrier-free" preparation is difficult to achieve. The specific activity of the radioisotope or radiotracer must be controlled for biochemical experiments on animals involving the determination of present environmental levels of trace metals. Table 7 summarizes typical theoretical and actual activities which were obtained (151). Table 8, derived from Sabbioni et al. (151), summarizes the estimated doses of several trace metals which should be administered to animals in order to assess toxicological effects at the environmental level. The requirement for very high specific activity radiotracers clearly demands the availability of high quality enriched target material. Examples of the cyclotron production of several trace metals for metallobiochemical and environmental toxicological investigations have been cited (152-161). Metabolic studies with ^{48}V (162,163), ^{74}As (154), and ^{107}Cd and ^{109}Cd (149) are cited as

TABLE 6. RADIOTRACERS CURRENTLY PRODUCED AT THE MILAN AVF CYCLOTRON AND ESSOR REACTOR OF THE JRC-ISPRA AND SUBJECTED TO ANALYTICAL CONTROLS FOR METALLOBIOCHEMICAL INVESTIGATIONS OF PRESENT ENVIRONMENTAL LEVELS OF METALS (Derived from reference 151).

Radiotracer	$T_{1/2}$	Production method	Biochemical applications
^{48}V	16 d	$^{48}Ti(p,n)$	Interrelationships between Fe and V metabolism
^{51}Cr	27.8 d	$^{51}V(p,n)$ $^{50}Cr(n,\gamma)$	Identification of Cr-binding components
^{59}Fe	45.1 d	$^{58}Fe(n,\gamma)$	Marker of non-heme and heme Fe-containing proteins
^{64}Cu	12.8 h	Szilard-chalm. on Cu-phtalocyanine	Exchange of Cu^{2+} with Cu-ceruloplasmin
^{65}Zn	245 d	$^{65}Cu(p,n)$	Metallothionein studies
^{69m}Zn	13.8 h	$^{68}Zn(n,\gamma)$	Metallothionein studies
^{63}Ni	80 y	$^{62}Ni(n,\gamma)$	Identification of Ni-binding components
^{71}As	2.5 d	$^{72}Ge(p,2n)$	Chemobiokinetics studies and cellular As-binding components
^{74}As	17.5 d	$^{74}Ge(p,n)$	
		$^{76}Ge(p,3n)$	
^{76}As	26.8 h	$^{75}As(n,\gamma)$	Simultaneous metabolic patterns of As^{3+} and As^{5+}
^{73}Se	7.2 h	$^{70}Ge(\alpha,n)$ $^{72}Ge(^{3}He,2n)$	Identification of Se-binding components
^{75}Se	120 d	$^{74}Se(n,\gamma)$	
^{110m}Ag	270 d	$^{109}Ag(n,\gamma)$	Metallothionein studies
^{107}Cd	6.7 h	$^{107}Ag(p,n)$	Metallothionein studies
^{109}Cd	1.3 y	$^{109}Ag(p,n)$	
^{115}Cd	43 d	$^{114}Cd(n,\gamma)$	Metallothionein studies

(continued)

TABLE 6. RADIOTRACERS CURRENTLY PRODUCED AT THE MILAN AVF CYCLOTRON AND ESSOR REACTOR OF THE JRC-ISPRA AND SUBJECTED TO ANALYTICAL CONTROLS FOR METALLOBIOCHEMICAL INVESTIGATIONS OF PRESENT ENVIRONMENTAL LEVELS OF METALS (Derived from reference 151).

(continued)

Radiotracer	$T_{1/2}$	Production method	Biochemical applications
^{113}Sn	119 d	$^{112}Sn(n, \gamma)$	Metallothionein studies
^{117m}Sn		$^{116}Sn(n, \gamma)$	
^{120m}Sb	6 d	$^{120}Sn(p,n)$	Metabolic patterns of Sb^{3+}, Sb^{5+} and Stibophen
^{122}Sb	2.7 d	$^{122}Sn(p,n)$	
^{124}Sb	60 d	$^{123}Sb(n, \gamma)$	Influence of the oxidation state, medium term experiments
^{123m}Te	119.7 d	$^{122}Te(n, \gamma)$	
		$^{123}Sb(p,n)$	
^{203}Hg	48 d	$^{202}Hg(n, \gamma)$	Metabolic patterns of organic and inorganic Hg simultaneously administered to the same animal
^{201}Tl	3 d	$^{201}Hg(p,n)$	Influence of the oxidation state, biliary excretion, transplacental transport
		$^{202}Hg(p,2n)$	
^{202}Tl	12 d	$^{202}Hg(p,n)$	
^{204}Tl	4 y	$^{203}Tl(n, \gamma)$	Metabolic patterns
^{203}Pb	2.17 d	$^{203}Tl(p,n)$	In vitro interaction of Pb^{2+} with genetic material
		$^{205}Tl(p,3n)$	
^{205}Bi	14.5 d	$^{206}Pb(p,2n)$	Metabolic patterns
^{206}Bi	6.4 d	$^{206}Pb(p,n)$	

TABLE 7. SPECIFIC ACTIVITY OF RADIOTRACERS PREPARED AT THE MILAN AVF CYCLOTRON FOR BIOCHEMICAL EXPERIMENTS ON LABORATORY ANIMALS INVOLVING PRESENT ENVIRONMENTAL LEVELS OF TRACE METALS (Derived from reference 151).

Radiotracer	Isotopic Target	Theoretical specific activity (μCi/ng)	(ng/ml) Conc.	Method of determination of carrier[1] [2]	Specific activity (μCi/ng)
^{48}V	^{48}Ti	161	198	NAA via ^{52}V	25
^{51}Cr	^{51}V	90.9	100	Diphenylcarbazide test	2
^{65}Zn	^{65}Cu	8.2	760	NAA via ^{69m}Zn	1.1
^{74}As	^{74}Ge	101	40	NAA via ^{76}As	(20
^{109}Cd	^{109}Ag	2.52	90	AAS, NAA via ^{115}Cd	0.47
^{120m}Sb	^{120}Sn	182	30	NAA via ^{122}Sb	64.5
^{201}Tl	^{201}Hg	217	<60	Rhodamine B	>40
^{203}Pb	^{203}Tl	298	830	AAS	5.9
^{206}Bi	^{206}Pb	99.5	<200	Cinchonine and KI test	>10

1 NAA = neutron activation analysis
2 AAS = atomic absorption spectroscopy

TABLE 8. ESTIMATED DOSES OF HEAVY METALS WHICH SHOULD BE ADMINISTERED TO LABORATORY ANIMALS TO INVESTIGATE LONG-TERM, LOW-LEVEL EFFECTS AT PRESENT ENVIRONMENTAL LEVELS (Reproduced from Reference 151).

Element	Estimated daily exposure for man						Suggested present environmetal levels (μg or ng/kg laboratory animal)		
	μg/70-kg standard man				Internal exposure (%)				
	Air	Smoke	Water	Food	Via diet	By inhal.	per os (μg)	By inhal. (ng)	By injection (μg)
V	0.06—3	~1	0.2—2	10—100	0.5(0.1—1)	20	0.1—2	0.5—60	0.0005—0.03
Cr	0.2—2	0.8—3	10—20	80—100	1.5(0.1—3)	20	1—2	3—70	0.01—0.05
Mn	0.002—12	~130	20—200	2500—3700	3(1—4)	20	30—60	0.3—2000	0.9—2
Co	0.02—0.06	~0.05	8—20	150—900	50(20—95)	20	2—15	0.3—2	1—7.5
Ni	0.07—3	0.4—1.5	0.04	300—600	5(1—10)	20	4—10	1—70	0.2—0.5
Cu	2—8	5—25	200	2300—3900	50(10—70)	20	30—60	30—450	15—30
Zn	2—60	5—15	500	13000—15000	> 70	20	180—220	30—1100	130—170
As	0.2—3	10—32	2	10—50	8(4—12)	10(5—16)	0.2—1	3—430	0.01—0.15
Se	0.06—0.2	0.01—2	0.04—1	60—150	70(50—90)	20	1—2	0.7—30	0.5—1.5
Mo	0.01—0.1	—	0.4—2	90—160	> 40	20	1—3	0.1—1	0.4—1.2
Ag	0.02—1	≈0.1	≈0.3	10—40	< 10	20	0.1—1	0.3—3	0.01—0.1
Cd	0.01—3.5	2—4	2—4	10—110	6(5—7)	15(10—20)	0.1—2	0.7—50	0.005—0.15
Sn	0.8—2	—	≈0.08	400—1700	< 10	20	5—30	10—60	0.5—3
Sb	0.03—0.7	0.1—0.8	0.04—0.6	7—60	< 10	20	0.1—1	0.7—20	0.01—0.1
Hg	0.4—1.5	0.1—0.5	0.08	5—20	50(7—95)	24	0.05—0.3	7—30	0.02—0.15
Tl	0.001—0.01	~0.1	0.006	~1.5	~30	~30	~0.02	~0.01—1	< 10
Pb	4—40	1—5	20	170—470	8(5—10)	40(30—50)	3—10	70—650	0.2—1
Bi	0.01—2	—	—	~60	< 10	20	~1	0.1—3	~0.1

specific recent examples.

It was not possible to determine the quantities of enriched stable target materials required in this category of biomedical research, but the demand for the radiotracers noted in Table 6 can probably be met by ORNL. Severe shortages could develop, however, if the toxicology of trace concentrations of the rare earths became the subject of more intensive research.

IV. Nuclear Magnetic Resonance (NMR), Electron Paramagnetic Resonance (EPR), and Mössbauer Spectroscopy in Biochemical, Biophysical, and Biomedical Research

Table 9 lists the requirements for enriched stable isotopes used in NMR, EPR, and Mössbauer spectroscopy in investigations of macromolecular dynamics, metal macromolecules, and metal functions in biochemistry. Of the isotopes listed, most biomedical research has been performed with ^{113}Cd, ^{111}Cd, ^{25}Mg, and ^{43}Ca in combination with high resolution NMR, and with ^{57}Fe in EPR and Mössbauer spectroscopy. There is a serious problem of an inadequate supply of isotopically enriched ^{113}Cd and ^{111}Cd, and possibly ^{43}Ca.

Armitage, Coleman, and collaborators (183-197) pioneered in the application of ^{113}Cd-NMR and ^{111}Cd-NMR as probes in biomedical research. The technique has been adopted by several laboratories (183-201), and applied in such areas as enzymology via metal ion activation in metabolism, protein and nucleic acid synthesis, hormone action, membrane structure, bone growth and metabolic regulation where Cd^{2+} is substituted for Ca^{2+}, and in investigations of the metabolism and toxic effects of heavy metals. For reviews, see references 255-258.

^{113}Cd-NMR has been used to determine the structure and function of more than 20 metalloproteins which are involved in a variety of metal-ion mediated biological processes (186,194,196). For example, the structure of metallothionein was unraveled by use of ^{113}Cd-NMR (257, 198). This mammalian protein is involved in the detoxification of heavy metals which man might ingest by environmental exposure (see Section III). Kurtz and co-workers (198) recently demonstrated that high resolution ^{113}Cd-NMR spectra (Fig. 5) of a solid decanuclear cation, cadmium (II) complex $[Cd_{10}(SCH_2CH_2OH)_{16}]$, overcame some of the limitations of ^{113}Cd-NMR in probing the structural and dynamic macromolecular solutions hampered by a fast exchange of Cd^{2+} with solvent and ligands. Their ^{113}Cd-NMR results correlated with the known structure of the cation (Fig. 6). Their data suggest that the ^{113}Cd-NMR resonances observed for metallothionein are due to CdS_4 coordination sites and not to $CdSO_4$ or CdS_3O_3 sites.

Recently, Welsh, Armitage, and Cooperman (201,259) have exploited the nuclear spin of $(\frac{1}{2})^{113}Cd$ to search for ^{113}Cd splitting of the ^{31}P signal of phosphoryl ligands bound to a complex of enzyme and $^{113}Cd^{2+}$. Figure 7 depicts the three sharp $^{113}Cd^{2+}$ NMR peaks that are observed when $^{113}Cd^{2+}$ is bound to the enzyme/yeast inorganic pyrophosphatase EC 3.6.1.1-(PPase) in the presence of inorganic phosphate (Pi). As none of the three peaks corresponds to $^{113}Cd^{2+}$ in solution, the investigators

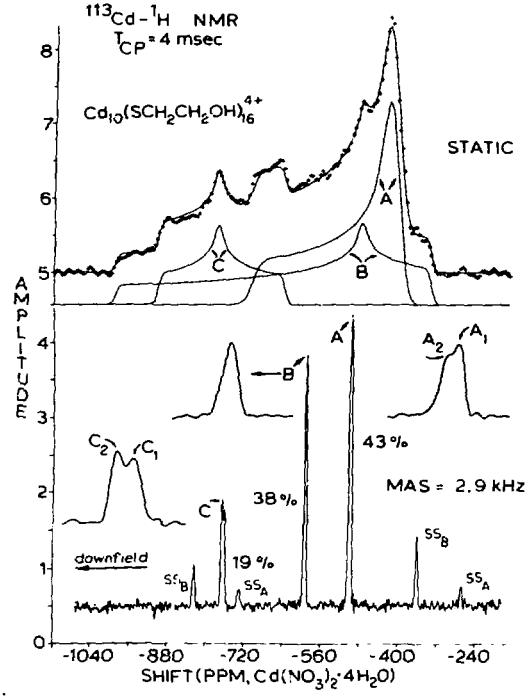

Fig. 5. $^{113}Cd-^{1}H$ CP NMR Spectra of Powdered $[Cd_{10}(SCH_2CH_2O\text{-}H)_{16}](ClO_4)_4$. (Top) Static Spectrum. "+" Indicates Actual Data Point; Solid Lines Indicate the Fitted Powder Patterns of Shielding Tensors for Each Resonance A, B, and C and Their Addition to Fit the Observed Spectrum. (Bottom) MAS Spectrum. Insets Show Resolution of Resonances A, B, and C.

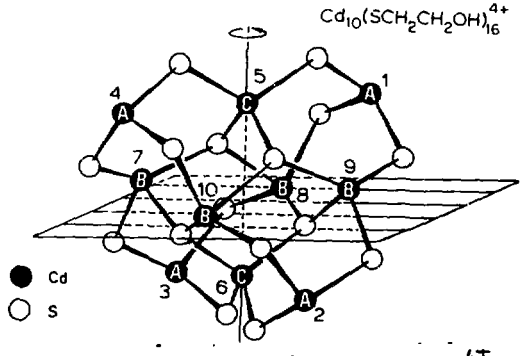

Fig. 6. The Cd-S Framework of $Cd_{10}(SCH_2CH_2OH)_{16}^{4+}$. The Lettering Indicates CdS_3O_3 (A), CdS_4O (B), and CdS_4 (C) Coordination Environments and Also Refers to the Assignments of Resonances in Fig. 5.

(Reproduced from reference 198 with permission of D. M. Kurz, Jr.)

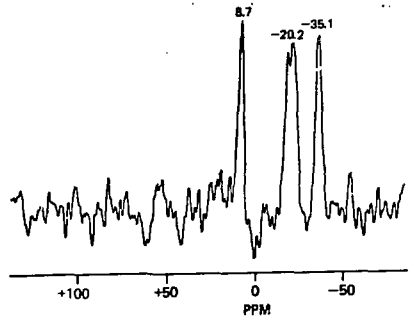

Fig. 7. ^{113}Cd NMR Spectrum of a Solution of PPase, $^{113}Cd^{2}$ and Pi. Total Concentrations, PPase, 2.1 mM (in subunits); $^{113}Cd^{2}$ 9.9 mM; Pi, 9.0 mM; pH 7.0, 25°C. Shifts are Reported with Respect to 0.1M Cd $(ClO_4)_2$. Resonance Frequency 19.96 MHz. (From K. M. Welsh, I. M. Armitage, and B. S. Cooperman, manuscript in preparation, reference 201 with permission, and reference 259.)

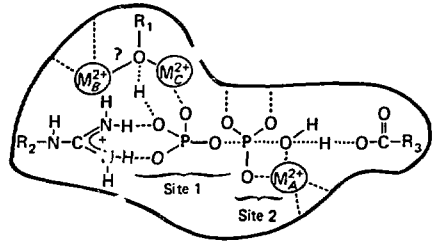

Fig. 8. A Possible Model of the Transition State for PPi Cleavage or Formation of PPase. The Heavy Solid Line Indicates the Protein Backbone. Dashed Lines Indicate Polary, Hydrogen, or Salt Bonds. Dotted Lines Indicate Bonds Which Are Being Broken or Formed During PPi Cleavage or Reformation. R_1 is a Hydrogen Atom or the Remainder of a Tyrosine Side Chain. R_2 is the Remainder of Arg 77. R_3 is the Remainder of an Aspartyl or Glutamyl Side Chain. (From K. M. Welsh, I. M. Armitage, and B. S. Cooperman, manuscript in preparation, reference 201 with permission, and reference 259.)

believe that the three peaks represent Cd^{2+} bound to each of the three divalent metal ion binding sites on the enzyme. Work is in progress (201) to replace a Cd^{2+} with a paramagnetic divalent metal ion to determine metal ion: metal ion distances. ^{113}Cd-NMR and other physical measurements and mechanistic features have lead to the formulation of a model (Fig. 8) for the transition state for PPase catalysis.

TABLE 9. STABLE ISOTOPES USED IN NMR, EPR, AND MOSSBAUER SPECTROSCOPY TO STUDY MACROMOLECULAR DYNAMICS, METAL MACROMOLECULE INTERACTIONS, AND METAL FUNCTIONS IN BIOCHEMISTRY.

Isotope	ORNL Sales Inventory* (g)	Projected Requirements
^{25}Mg	1	0.2-1
^{29}Si	9	0.1-0.5
^{33}S	0.3	0.2
^{34}S	2.7	0.2
^{43}Ca	0.6	4
^{57}Fe	18.5	5-8
^{63}Cu	14.5	0.2
^{71}Ga	0.5	0.3-1
^{77}Se	0.17	2-5
^{95}Mo	4	0.3
^{111}Cd	0	3-10
^{113}Cd	0	3-10
^{125}Te	6+	0.3
^{183}W	0	0.3
^{195}Pt	0.2	0.5-1
^{199}Hg	0.3	0.3-1
^{203}Tl	0+	0.1-1
^{207}Pb	1.5+	0.1-0.5

+ ORNL separation in progress
* Sales Inventory as of December 18, 1981

Many proteins and enzymes contain sulfhydral groups essential to their biological activity. ^{33}S-NMR would be popular were it not for the 0.74 percent natural abundance of ^{33}S, and the relatively low sensitivity (2.26×10^{-3} relative to the proton) of NMR for the ^{33}S-nucleus. In many instances, selenium can be substituted for sulfur without loss of biological activity. The ^{77}Se nucleus offers adequate NMR sensitivity (6.9×10^{-3} relative to the proton), possesses a large chemical shift range (~2,000 ppm), and is very sensitive to its electronic environment (see references 202-206 and the references contained therein). Odom and co-workers, for example, are using selenium in modification studies of biological macromolecules, such as ribinonuclease-A and lysozyme (260), to ascertain the feasibility and utility of ^{77}Se-Fourier transform (FT)-NMR (202). Their (206) approach is to design reagents which will incorporate selenium covalently into enzymes by reaction with sulfhydral groups to form selenenyl sulfides (205). A series of model compounds (203,206), such as selenenyl sulfides, dialkyli selenides, dialkyl diselenides, selenols, selenonium compounds, and seleno-oxyacids have been synthesized and the ^{77}Se chemical shifts, or spin-lattice relaxation times, characterized. ^{77}Se-FR-NMR may lead to an understanding of the pKa of the ionizable group and information on the pH effects at a catalytic enzyme site containing selenium (203). For example, thymidylate synthetase, which catalyzes the reductive methylation of dUMP to yield dTMP, loses its activity after modification of its catalytic sulfhydral group. The reagent 6,6'-diselenobis-(3-nitrobenzoic acid) was used to study the rate of inactivation of thymidylate synthase at two pH values (205). The ^{77}Se-FT-NMR technique should be readily amenable for both characterization and kinetic studies of small selenium substrates interacting with a macromolecule (204).

Roberts (208,209) has reported ^{199}He-NMR of organomercurials and their adducts with amino acids and ribonuclase. Her results indicate that enriched ^{199}Hg will be required to have the necessary sensitivity for the study of protein (phospholipase-As)/ethyl mercury phosphate (EMP) and nucleic acid/EMP complexes where sample solubilities are <1 mM.

Examples of other metal-NMR investigations in biomedical research are cited for Mg (210-212,214,215), Ca (211-215), Fe (224), Pt (216-218), and W (219).

The fundamental importance of biological nitrogen fixation has focused mainly on the nitrogenase complexes from Azotobacter Vinelandii. The Azotobacter nitrogenase protein components molybdoferredoxin (Mo-Fe) and azoferredoxin (Fe) can be enriched selectively with ^{57}Fe or ^{95}Mr. The metal compositions and structures have been probed with EPR and Mössbauer spectroscopy (220-223,225-229).

The chemical identity of iron in seeds and bran from wheat grown in ^{57}Fe-enriched culture medium and of solid ferric phytates has been studied by Mössbauer spectroscopy (231). Clarification of the chemical nature in situ of the iron in bran might aid in explaining the action of bran on iron absorption. (See bioavailability studies in Section II.)

Maeda et al. (207) have reported Mössbauer studies on oxygen and carbon monoxide binding to the hemeiron in myoglobin. Other

biomedical related investigations employing Mössbauer spectroscopy are discussed in references 230 and 232.

V. Advances in Radioactive and Non-radioactive Tracer Technology

Activable isotopes find occasional use in biomedical research. Chromium-50 has been used in kinetic studies of erythrocyte survival in infants and pregnant women (233-238) where the use of radioactive tracers would be unethical. Iron-58 is applicable to studies of iron utilization in pregnant women (236). Investigators have noted that enriched ^{74}Se and ^{41}K may be utilized in the future as activable tracers (235).

Enriched stable isotopes have been routinely used for calibration of instruments to assure high accuracy trace determination of isotopic concentrations of a variety of biological materials and health standards (239-248).

A liquid-emulsion microautoradiographic technique utilized ^{45}Ca, ^{95m}Tc, and ^{96}Tc for investigations of the growing kinetics of long bone in young rabbits (249,250).

A proposed radioisotope-based computerized tomograph (CT) utilized three rotating 12 Curies, ^{153}Gd ($T_{1/2}$ = 241 d) sources, which emit about equal intensities of 42 and 100 keV photons, to permit monochromatic dual energy ultra-accurate tomodensitometry measurements of the body (251-253). The isotope-source based CT scanner was designed for space flight in order to measure bone mineral metabolism, cardiac output, etc. (254). The natural abundance of ^{153}Gd is only 0.2 percent, and therefore the enriched stable isotope is required.

Conclusions

The Isotope Separation Facility at Oak Ridge National Laboratory is the only reliable source of electromagnetically separated enriched stable isotopes for biomedical research in the free world. The Soviet Union is an alternate supplier (West Germany and Israel are minor suppliers), but dependence on foreign governments would be risky since the supply of materials required to keep America at the forefront of science and technology could be reduced or cut off at any time.

Biomedical research was classified into five categories: (1) medical radioisotope production, labeled compounds, and potential radiopharmaceuticals; (2) nutrition, food science, and pharmacology; (3) metallobiochemistry and environmental toxicology; (4) nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and Mössbauer spectroscopy in biochemical, biophysical, and biomedical research; and (5) miscellaneous advances in radioactive and non-radioactive tracer technology. Item (1) requires a source of 10-50 milligram quantities of stable isotopes at various isotopic enrichments in order to investigate the radiochemistry and production routes for the introduction of "new short-lived" radioisotopes into nuclear medicine. Ultrahigh isotopic enrichment is often required in order to optimize production yields and radioisotopic purity. Once the optimum nuclear reaction and conditions

have been determined, the requirements for specific stable isotopes may increase by a factor of 100-1,000 within a 10-year period. Research in (2) and (4) generally relies only on stable isotopes, whereas (3) relies most heavily on derived longer-lived radioisotopes. New areas of biomedical research (5) can be explored only if enriched stable isotopes and radioisotopes derived from them are available.

Acknowledgments

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A sincere effort was made to locate and contact all American investigators with enriched stable isotope requirements meeting the criteria of this study. The scientists who responded to the survey which was conducted by letter and telephone are acknowledged with appreciation in Appendix Appendix I.

Appendix II was provided to the Panel at the Workshop by Professor Y. Murakami, Department of Chemistry, Tokyo Metropolitan University. The table identifies the enriched isotopes used for research in Japan as purchased by the Japan Radioisotope Association during the period April 1977 to December 1981.

Appendix I

List of scientists who responded to the survey of laboratory or institutional requirements for enriched stable isotopes. A copy of the survey letter follows the listing.

Dr. Roger Aamodt, National Institute of Health
Dr. Kenneth G. D. Allen, Colorado State University
Dr. Ian M. Armitage, Yale University
Dr. Robert Ayres, National Bureau of Standards
Dr. M. W. Billinghurst, Health Science Center - Winnipeg
Dr. Mauro Bonardi, Istituto di fisica, Milan
Dr. Thomas H. Brown, University of Illinois
Dr. Robert Bryant, University of Minnesota
Dr. Thomas F. Budinger, Donner Laboratory
Dr. Chris Cann, University of California - San Francisco
Dr. Britton Chance, University of Pennsylvania
Dr. Joseph E. Coleman, Yale University
Dr. Barry S. Cooperman, University of Pennsylvania
Dr. James J. Dechter, University of Alabama
Dr. Donald B. Denny, Rutgers University
Dr. Richard Ehrenkaufer, University of Michigan
Dr. Geoffrey Eichholz, Georgia Institute of Technology
Dr. Paul Ellis, University of South Carolina
Dr. Ralph Fairchild, Brookhaven National Laboratory
Dr. P. V. Fennessey, University of Colorado
Dr. Ronald Finn, Mt. Sinai Medical Center - Miami
Dr. Richard W. Fink, Georgia Institute of Technology
Dr. Sture Forsen, University of Lund
Dr. Hans Frauenfelder, University of Illinois-Urbana
Dr. Carleton D. Gajdusek, National Institute of Health
Dr. Otto A. Gansow, Michigan State University
Dr. Bernard C. Gerstein, Iowa State University
Dr. Howard J. Glenn, M.D. Anderson Hospital - Houston
Dr. G. A. Glomski, SUNY - Buffalo
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September 24, 1981

[1]

Dear [1]

You have been identified as a researcher that can provide vital information for a workshop on the Applications of Stable Isotopes and Derived Radioisotopes being organized by the National Research Council under the aegis of its Subcommittee on Nuclear and Radiochemistry. The workshop is a response to a request from the Office of Basic Energy Sciences (OBES) of the U.S. Department of Energy. The OBES would like documentation from the user community on recent past, present and projected applications of, and requirements for, electromagnetically separated stable isotopes used in biomedical, chemistry and physics research, clinical medicine and for industrial applications.

I have been asked to gather information on everything falling within the broad definition of biomedical research, e.g. medical isotope production, radiopharmaceutical and preclinical research, NMR (with electromagnetically separated isotopes), activable tracers, etc. The task is somewhat amorphous. Your input is important.

Goals include the generation of the report which summarizes the needs and uses of enriched stable isotopes and which makes quantitative estimates of the quantities required today and for your future research programs. Pertinent preprints, reprints, or references to your recent publications and current reviews would be helpful.

Would your research be significantly impaired if certain isotopes (which ones) were temporarily or permanently unavailable from Isotope Sales at Oak Ridge? The possibility could exist as early as 1983, hence one reason for the workshop.

Would you identify other scientists (name/address/phone number) that can provide information. We will appreciate receiving your input in writing, preferably by October 19th.

Thank you very much for your cooperation in this effort.

Sincerely yours,

Richard M. Lambrecht

RML:ns

Appendix II

The quantity (milligrams), the number of pieces, and the cost of representative enriched isotopes which were used principally during the period April 1977 to December 1981 in Japan. The materials were imported from ORNL through the Japan Radioisotope Association. Information kindly provided by Professor Y. Murakami, Department of Chemistry, Tokyo Metropolitan University.

	No. of Mgs	No. of Pieces	Price/ Mg	Cost/ Isotope
^{121}Sb	780	3	$1.40	$10,920
^{138}Ba	1,800	2	0.10	150
^{113}Cd	3,014	7	-	-
^{114}Cd	4,880	9	0.45	2,684
^{40}Ca	1,650	3	0.30	495
^{160}Ce	3,010	5	0.05	150
^{37}	200	5	7.40	1,480
^{50}Cr	2,127	11	5.35	11,280
^{63}Cu	1,420	15	0.15	213
^{164}Dy	7,400	4	0.25	1,850
^{166}Er	1,280	4	0.20	256
^{170}Er	1,100	3	0.30	330
^{151}Eu	3,500	8	0.45	1,602
^{160}Gd	25,970	6	0.90	23,373
^{71}Ga	100	-	0.85	85
^{70}Ge	1,880	5	-	-
^{74}Ge	1,330	4	0.15	200
^{180}Hf	300	3	1.35	405
^{58}Fe	17,100	12	0.10	1,710
^{138}La	9	9	40.45	364
^{208}Pb	4,919	12	0.35	1,721
^{176}Lu	17	3	-	-
^{24}Mg	4,580	12	0.35	1,603
^{92}Mo	1,400	4	0.30	420
^{142}Nd	1,980	10	1.85	3,608
^{150}Nd	1,442	6	1.20	1,730
^{60}Ni	18,160	13	0.25	4,540
^{58}Ni	16,315	16	0.35	5,510
^{192}Os	300	2	-	-
^{105}Pd	2,000	1	-	-
^{108}Pd	300	2	0.70	210
^{196}Pt	1,300	6	-	-
^{41}K	250	5	6.40	1,600
^{87}Rb	3,548	13	3.50	12,418
^{102}Ru	180	3	-	-
^{104}Ru	140	2	0.90	126

Appendix II, cont.

	No. of Mgs	No. of Pieces	Price/ Mg	Cost/ Isotope
^{154}Sm	2,400	5	0.15	360
^{152}Sm	2,580	6	0.15	387
^{80}Se	300	6	0.90	270
^{28}Si	1,800	6	0.85	1,530
^{109}Ag	1,400	6	0.60	840
^{88}Sr	4,500	5	0.15	675
^{34}S	890	8	3.25	2,893
^{130}Te	3,703	6	0.25	740
^{119}Sn	11,054	16	0.35	3,869
^{48}Ti	1,165	2	0.30	350
^{182}W	300	2	0.30	90
^{174}Yb	2,000	3	0.25	500
^{50}V	1	1	121.15	121
^{64}Zn	3,110	8	0.45	1,400
^{90}Zn	1,450	4	0.95	1,388
	292,279	866		$95,945

Summary

46 elements; 192 nuclides:
Total 292,279 mg; 866 pieces
Average 5,220 mg/month; 16 pieces/month
$3,000/month (estimated)

Example of Usage of Some Isotopes

A. Industrial needs:
Te, Mo, Tl, Ni

B. Toxic environmental pollutant:
Bi, Pb, Tl, Hg, Sb, Sn, Cd, Ag

C. Essential element metabolism:
Mo, Se, Zn, Cu, Ni, Co, Mn, Cr, V, Kb, Ca, Mg, Cd

D. Isotopes used for NMR, ESR, Mössbauer spectroscopy, and other research:
^{25}Mg, ^{29}Si, ^{33}S, ^{43}Ca, ^{57}Fe, ^{63}Cu, ^{71}Ga, ^{77}Se, ^{95}Mo, ^{111}Cd, ^{113}Cd, ^{125}Te, ^{183}W, ^{195}Pt, ^{199}Hg, ^{203}Tl, ^{207}Pb

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APPENDIX 8

WORKSHOP ON CLINICAL APPLICATIONS OF STABLE ISOTOPES AND DERIVED RADIOISOTOPES

Richard C. Reba, M.D.

Nuclear medicine uses enriched stable isotopes in at least three ways: (1) directly as stable isotope tracers; (2) incorporated into a chemical substrate or precursor to serve as isotope tracers; and (3) as target material for the production of radioactive isotopes. What we are primarily concerned with in nuclear medicine, except for the isotopes of lithium and boron, are those materials in the periodic table of $Z \geq 12$, i.e., magnesium and up. My role is to summarize the importance of the stable isotope program for the practice of clinical nuclear medicine. A precise translation of this charge is to justify the existence of nuclear medicine--i.e., why should clinical nuclear medicine continue to be practiced, since without stable isotopes and the target materials from which the radioactive isotopes are derived, nuclear medicine would not exist? Continued funding should be based on results--what has been accomplished in the past, what is being accomplised now (efficacy), and what are the probabilities for continued success in the future?

In this regard, let me digress for a moment. The chairman of the board of the Blue Shield Association is quoted as saying that "it is clear that those who pay the bills to the third parties and to the government are not going to accept financial responsibility for procedures simply because they are innovative and noninvasive. Nor will the cost of technically complex and elegant equipment be accepted unless it can be clearly demonstrated that its use benefits patients."

The director, a practicing radiologist, went on to say that the Blues realize that they have undertaken an enormous project in studying the medical necessity of the imaging procedures. "Even though we must be selective," he said, "there is a tremendous amount that deserves to be considered." One of the medical strategies that he expects to be examined will be the scanning of women who have been treated for primary breast malignancy and who are completely free of symptoms. "The literature is full of articles recommending that such asymptomatic patients be checked at least annually," the director said. "For several years I have corresponded with authors of papers recommending such scanning, posing a simple question: what evidence is there that the prognosis has changed in any way if metastatic disease is diagnosed

before symptoms develop rather than after the patient becomes symptomatic? I have yet to get any such evidence and, therefore, must conclude that such scanning is not of value to patients." Blue Shield has estimated that the savings to the U.S. public from the elimination of annual bone scans for asymptomatic post-mastectomy patients would be at least $100 million annually.

The discipline of nuclear medicine has become a significant contributor to health care in America. Examinations by means of radioactive tracer methods are of great importance in the diagnosis of abnormalities and diseases of the lung, heart, liver, spleen, kidney, central nervous system, skeleton, and thyroid gland. Imaging of the skeletal system, for example, provides the earliest and most sensitive indication of a pathologic lesion in bone of any diagnostic method routinely available today. This nuclear medicine test is useful in both hospitalized and non-hospitalized patients, and is an important early indicator of cancer that has spread to bone. Therefore, this test is important in the planning, execution and evaluation of therapy in patients in whom the diagnosis of cancer has been established.

Nuclear medical techniques are also used to determine specific physiological functions. Such examinations include, for example, measurements of cardiac output, thyroid function, and vitamin, fat, and mineral absorption from the gastrointestinal tract.

The widespread application of nuclear medicine is shown by the fact that about 17,000 million invivo and perhaps 100,000 invitro nuclear medicine studies were performed during 1980. This corresponds to about one out of every two or three hospitalized patients plus a large number of outpatients (perhaps 275,000 a day) for whom the diagnosis and management of disease relies heavily on the results of radiotracer studies. Clearly, this discipline has evolved to the point where it affects a large segment of the public. If the clinical indications for requesting a nuclear medicine examination are related to the requests for laboratory and radiologic testing, then approximately one-third are obtained in order to help make a diagnosis, one-third to evaluate response to therapy and the remainder to record objective temporal changes of a disease process.

Invivo diagnosis is carried out with small amounts of radioactivity that are administered to the patient, followed by external measurements to image an organ or the internal distribution of the administered drug. Invitro studies involve an analysis of a blood or urine specimen for a specific component, using a radioactive substrate.

Two major national organizations represent the nuclear medicine worker: the American College of Nuclear Physicians, comprised of more than 1,200 physicians and scientists in the active practice of nuclear medicine, and the Society of Nuclear Medicine, which is composed of about 11,000 physicians, technologists, engineers, chemists, physicists,

pharmacists, and computer scientists involved in the delivery of nuclear medicine services. Some members of the American College of Radiology, the College of American Pathologists, and the American College of Nuclear Medicine are also involved in the practice of nuclear medicine to varying degrees.

Nuclear medicine is now a defined medical specialty. In 1971 the American Board of Nuclear Medicine (ABNM) was established as a conjoint board by the American Board of Internal Medicine, the American Board of Radiology, the American Board of Pathology, and the Society of Nuclear Medicine after approval by the AMA House of Delegates following recommendations by the American Board of Medical Specialists and the Council of Medical Education of the AMA. During its first five years the ABNM certified more individuals than ten other boards combined, and by 1980 the Board has certified a total of 3,070 individuals. During 1980, more individuals were certified than in any year since 1976, and most of those were graduates of American medical schools. Dr. Joseph Ross, president of the ABNM, estimates that there are 3,000 to 4,000 additional physicians who devote a significant proportion of their professional effort to nuclear medicine but are not certified by the ABNM. Preliminary data collected by the Nuclear Medicine Delphi Panel of the Department of Health & Human Services reveal that currently there are about 3,800 full-time equivalent (FTE) nuclear medicine practitioners, but that the total number of individuals practicing nuclear medicine is much higher, perhaps on the order of 22,000. The working estimate for 1990 is 5,038 FTE specialists.

It also may be interesting to note that most of those who were practicing nuclear medicine 20 years ago had originally been trained in some other specialty, usually radiology, internal medicine, or pathology. Today, 30 to 40 percent of those being certified are trained primarily in nuclear medicine.

The solution of almost every serious medical problem in patients sick enough to be hospitalized may be facilitated to some degree by a nuclear medicine study. Although the practice of nuclear medicine includes the use of radioisotopes, for both diagnostic and therapeutic purposes, the emphasis is to a large part on diagnosis. But, the term "diagnosis," as used here, is a broad term that is not restricted simply to the identification or classification of a specific disease process (see Table 1).

TABLE 1. USES OF NUCLEAR MEDICINE TESTS

1. Patient Management
   A. Identify disease etiology
   B. Disease screening (high sensitivity and limited specificity)
   C. To monitor response to a therapeutic intervention
   D. To record the natural history of a disease process
2. Clinical Research
   A. Provide new knowledge
   B. Modify existing knowledge

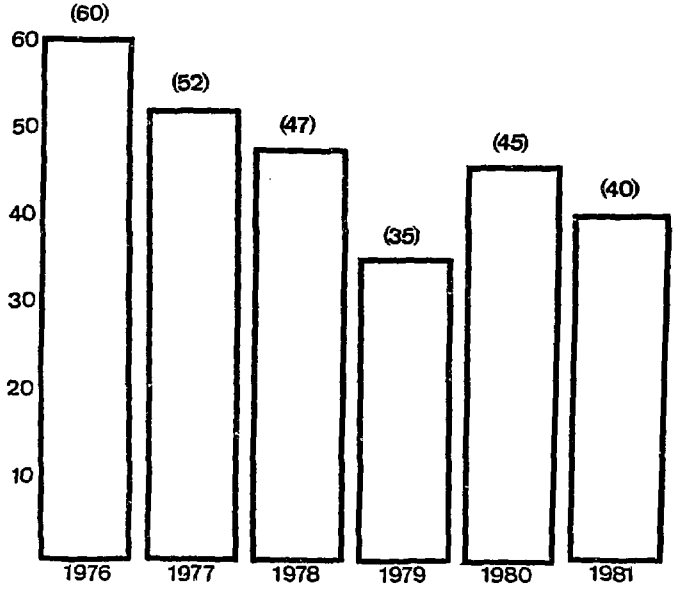
In general, diagnostic nuclear medicine procedures are not invasive and present little risk to patients. Furthermore, they are relatively inexpensive when compared to alternatives. It should be remembered that total expense should include the dollar cost to the patient, physical and emotional discomfort, physical inconvenience, the time lost of the patient, and the time of the physician. With reference to obvious risk, the Subcommittee on Adverse Radiopharmaceutical Reactions of the Society of Nuclear Medicine reports a possible incidence of $1:10^5$ administrations over the past six years, and the data indicate that this low incidence is falling (Table 2).

TABLE 2

Number of Adverse Reactions

Per Year

FROM SNM



Nuclear medicine studies provide information on the initial diagnosis and the progress of disease, and are used to assess the effect of therapies. In some instances the nuclear medicine examination is unique in its ability to provide the information needed for proper and complete clinical management. In patients with pulmonary embolism the effects of intraluminal clots are readily apparent through nuclear medicine techniques, unlike x-ray studies. In examinations of the kidney, nuclear medicine studies are found useful in the evaluation of the transplant recipient. In the practice of pediatrics, the follow-up of children with congenital obstructive uropathy utilizes nuclear medicine procedures to minimize gonadal radiation exposure once the diagnosis and anatomy are well defined. Bone scans are helpful in the management of patients in whom the diagnosis of cancer is established and in children to make the early diagnosis of congenital hip disease. Cardiac studies provide left ventricular perfusion and ejection fraction in a convenient way so that the function and integrity of cardiac muscle may be known. Nuclear cardiology studies are also used to evaluate drug-induced cardiomyopathy. New hepatobiliary radiopharmaceuticals are useful in studies of newborns with congenital and progressive jaundice, a life-threatening disease.

Alternate techniques to provide the information noted above are more invasive, resulting in increased risk and increased costs. All nuclear medicine studies may be performed at outpatient facilities, a fact that makes them particularly apt for use with poor patients or those who live in rural areas where direct access to advanced technology is not possible. While brain scans utilizing radiotracers constitute perhaps less than 5 percent of all scans in a hospital with a CT scanner, brain scans comprise 25 to 30 percent of the nuclear medicine procedures performed in areas where CT is not present.

How effective are nuclear medicine procedures? Should the specialty of nuclear medicine continue to exist? What benefits have been realized by the public from the clinical utilization of nuclear medicine tests?

Because many nuclear medicine tests are highly sensitive indicators of abnormal structure or function, they reduce the time interval from the onset of symptoms to final diagnosis and, therefore, reduce patient discomfort. Unlike the traditional or new static radiologic procedures, which display x-ray density or absorbance--i.e., whether a structure, displayed as a shadow, is or is not present--nuclear medicine has the capability of precisely quantifying regional organ or tissue function. Using these methods, one can determine the amount and rate of blood flow to an area (separate renal, pulmonary, or cerebral blood flow), whether an organ has increased or decreased function even though structural integrity has been maintained (thyroid, left ventricular function), or even when a group of common cells, such as nuclei in the brain, can metabolize glucose efficiently. It is now possible, in short, to discover regional functional abnormalities even when the overall function-

ing of an organ remains within normal limits and anatomical structure appears normal.

Clinical nuclear medicine is perhaps the best example of rapid transfer of government supported basic research to the private commercial sector and to the general public. Various people have estimated that all the funds spent by the federal government on nuclear medicine research have more than paid for themselves with the benefits derived from their use in the practice of medicine. The interdisciplinary nature of nuclear medicine, which encourages communication among a number of different basic science and clinical science disciplines, is the reason for this rapid transfer.

I will now offer several specific examples to support these statements.

Nuclear Cardiology. Between 1969 and 1977 there was a 22 percent decrease in mortality from coronary artery disease (CAD) among men in the United States, and a 27 percent reduction among women. Yet one of every six Americans is said to have heart or blood vessel disease, and many have no symptoms until it is too late to do anything about it. CAD is still epidemic in the Western world, and the principal cause of death in middle-aged men. (Mortality from this disease is increasing in communist countries, particularly in Poland, where the increase has been 65 percent during the past 10 years.) It has been estimated that heart attacks kill approximately 70,000 people per year in the United States.

Once CAD is identified, however, therapy is available to treat the disease. Nuclear medicine methods of cardiological diagnosis are being applied with increasing frequency in outpatient facilities to screen men and women for the presence of heart disease, to document or reject diagnosis in patients with atypical symptoms or atypical cardiographic tracings, to evaluate drug or surgical therapy, to establish prognosis by categorizing a post-myocardial infarct patient as high or low risk, to evaluate drug toxicity, and to distinguish CAD from other types of heart disease in patients having mitral valve prolapse, aortic stenosis, idiopathic cardiomyopathy or cardiomyopathy from diabetes mellitus, sarcoidosis, periarteritis, lupus erythematosis or thyroid disease (Tables 3 & 4, data from W. Adams, et al). An additional important use of these tests is in deciding which patients should be admitted or retained in a costly intensive care facility.

TABLE 3

THALLIUM 201 EXERCISE TESTS: SIGNIFICANT CORONARY STENOSIS

	N	201 Tl		E C G	
		Sensit.	Specific.	Sensit.	Specific.
1980 POHOST (MULTIPLE CENTERS, USA)	1077	82%	90%	61%	82%
1980 SIMOONS HUGENHOLTZ	118	75%	86%	59%	76%
1980 SAUER, SEBENING	120	91%	94%	-	-
1980 LÖSSE, LOOGEN	169	99%	69%	79%	69%
1981 HÖR (MULTIPLE CENTERS)	3092	83%	90%	-	-

TABLE 4

RADIONUCLIDE VENTRICULOGRAPHY EXERCISE TESTS: SIGNIFICANT CORONARY STENOSIS

	Sensit.	Specific.	
1977 BORER et al	94%	91%	Global EF
1979 BODENHEIMER et al	91%	87%	Reg. Wall Mot.
1980 CALDWELL, HAMILTON	93%	55%	Global EF
1980 NOLAN et al	89%	88%	Reg. Wall Mot.
1980 SAUER, SEBENING	83%	100%	Reg. Wall Mot.
1981 ADAMS et al	93%	100%	Reg. Wall Mot.

One other topic should not be ignored, and that is the relationship between nuclear cardiology studies and other tests of cardiac function and structure. A complete description of these interprocedural relationships at the Johns Hopkins Hospital since 1973 has been done by Dr. Henry Wagner. There has been a progressive increase in numbers of echocardiograms and exercise electrocardiograms, while phonocardiography, the recording of heart sounds, experienced a dramatic fall-off (Fig 1). When compared to the noninvasive nuclear cardiology studies, the number of adult cardiac catheterizations at Hopkins increased at the same time as did the noninvasive studies. Seventy-three percent of the cardiac catheterizations were for CAD and reflect the tremendous impact of coronary artery bypass grafting. The parallelism between the changes in the numbers of catheterization studies and cardiac surgery is also apparent (Fig. 2-4). The Johns Hopkins data courtesy of H.N. Wagner, Jr., M.D.

FIGURE 1

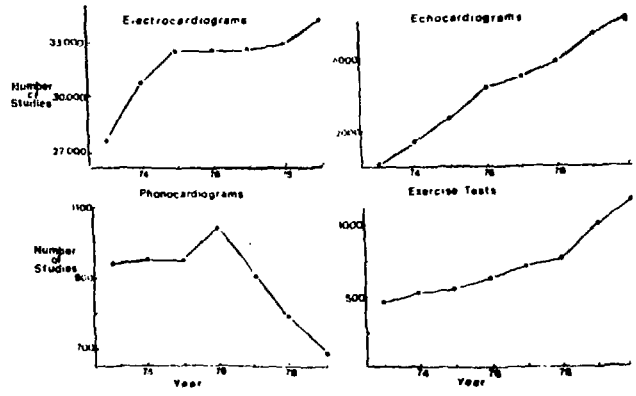


FIGURE 2

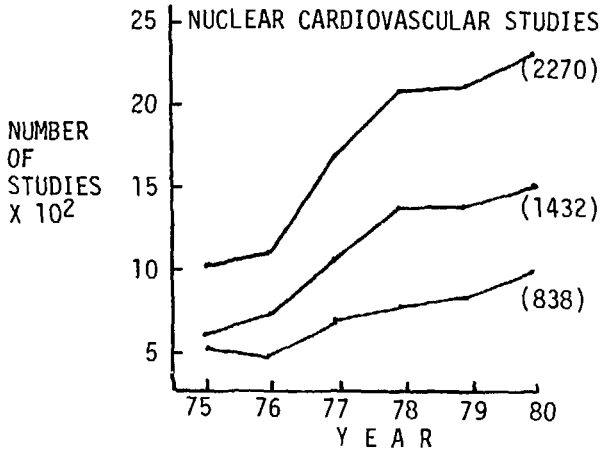


FIGURE 3

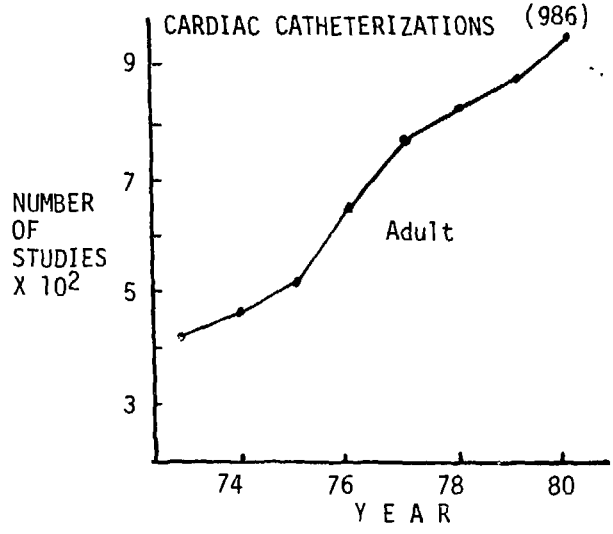
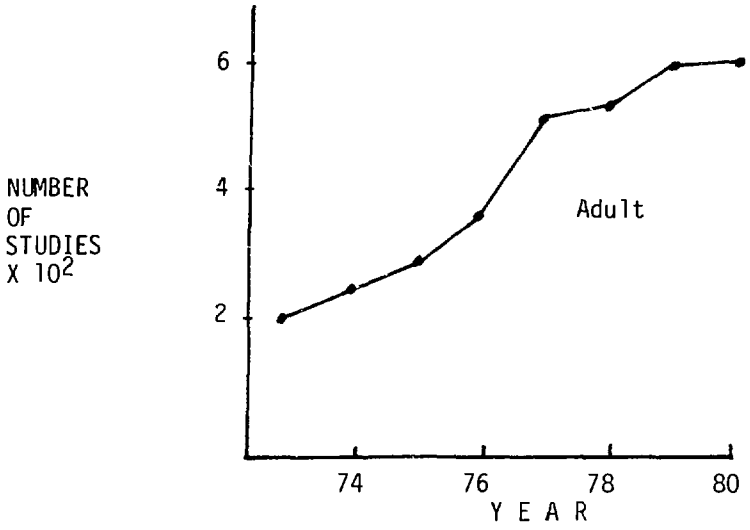


FIGURE 4

OPEN HEART SURGERY



There are many examples of clinical presentations of cardiac symptoms that defy immediate and exact diagnosis. Even after thorough physical examination and preliminary cardiac testing, the integrity of the coronary arteries remains uncertain. Because it is impossible for cardiac catheterization facilities to fill the diagnostic needs of the public, it is important to continue to refine relatively uncomplicated noninvasive tests.

Nuclear cardiology tests result in a better selection of patients for cardiac catheterization. Data on patients at Johns Hopkins indicate that the ratio of patients who progressed from cardiac catheterization to cardiac surgery changed from 1:2 in 1975 to 2:3 in 1979. The number of negative cardiac catheterizations in women has been reduced from 57 percent to 10 percent, and in men less than 50 years old from 25 percent to 10 percent. Our data from the George Washington University Hospital are not as complete as those at Hopkins but, in general, our improvement in percentage terms has been dramatic (Table 5).

What can a patient expect after surviving an acute myocardial infarction? It is known that of 100 patients who leave the hospital, 10-20 will die within one year, 5-6 will suffer a re-infarction but recover, while no less than 25 will develop angina pectoris. Which ones, then, should have a coronary angiography? That is, who should be evaluated for coronary artery bypass surgery? The best evidence to date suggests that left ventricular dysfunction, easily determined by nuclear studies, is the most reliable method of identifying high-risk patients.

TABLE 5

GEORGE WASHINGTON UNIVERSITY HOSPITAL
NUCLEAR CARDIOLOGY STUDIES

	1977	'78	'79	'80	'81	'82 Est
Pyrophosphate	116	178	105	133	63	19
Thallium	0	0	71	250	161	118
Gated Blood Pool	0	0	46	497	948	1162
Cardiac Catheterization	292	358	488	406	467	540
Cardiac Surgery	55	75	117	212	201	-

TABLE 6

RADIONUCLIDES USED IN NUCLEAR CARDIOLOGY

Radium-C; P-32; Na-24; I-131; Hg-197, 203

Cesium-129, 131, 133, 134

Rubidium-81, 82, 84, 86

Postassium-42, 43

Technetium-99m

Indium-113m

Barium-137m

Iridium-191m

Thallium-201

C-11, N-13, O-15, F-18, In-111, I-123

Table 6 shows that many other isotopes were used before Tl-201. Evaluation using many of these radionuclides required enriched stable isotopes. Although the biological precursors of Tl-201 have been discarded, enough new physiological information was revealed during the use of each to encourage physicians and scientists to seek other radionuclides with more desirable nuclear properties. Without these earlier clinical investigations, the place of Tl-201 in the present practice of nuclear cardiology would not be what it is.

It should be mentioned here that there are many radionuclides, such as ^{201}Tl, that can be produced without using an enriched target. However, once a radionuclide has been demonstrated to be clinically useful, it becomes necessary to use the maximal practical enriched target in order to maximize the yield. It is possible to perform certain research projects using impure radionuclide preparations in subhuman species, but chemical contamination will frequently interfere with biological distribution and radiolabeling, and radiochemical contamination will interfere with external detection and quantification. When Dr. Paul Harper first used radioactive thallium, the material was really a mixture of radioactive nuclides. Although this "radiogemish" was suitable for the purpose of exploring a potassium analog as a myocardial imaging agent, it was not adequate for clinical use. Brookhaven then developed the now universally used production method. Since the quality and cost of the radionuclide product is a function of several factors--e.g., the incident particle energy, the composition and thickness of the target, the time of bombardment, and the efficiency of target recovery--enriched nuclides are required so that the nuclear and chemical characteristics can be evaluated with respect to production processes, expected yields, side reactions, impurities, etc.

A similar story can be told about Tc-99m. Although fission moly was used in the first animal and patient studies using ^{99}Mo and then ^{99m}Tc, the early commercial product was made by neutron irradiation of enriched $^{98}Mo(n,g)\ ^{99}Mo$. This material was suitable for clinical use. Later, with the development of cold radiopharmaceutical kits and the requirements for chemical purity and high specific concentration (which is also necessary for the small volume bolus injections being used for flow studies), the ^{99}Mo source reverted to the fission product material. The present ^{99}Mo and ^{99m}Tc market in the United States is estimated to exceed $100 million annually.

Because of differences in local preferences, it is difficult to extrapolate from what is done at a small number of hospitals to the country at large. This is so even among hospitals of a like kind. Compare the relative frequency of the different nuclear cardiology studies performed at Johns Hopkins (approximately 1,000 beds), Figure 3, with those performed at George Washington (510 beds) in Table 5.

Some indication of the growing use of thallium, however, can be

found in Table 7, which shows the number of gallium and thallium tests performed at 57 VA hospitals from 1977 through 1980. Other VA hospitals are not included because they did not perform the tests or their files were missing or incomplete. The numbers are actually for patient visits, which should approximate the number of patients studied. Smaller VA hospitals contributed smaller numbers to the overall results, which are probably skewed by data from larger VA centers.

TABLE 7

YEARLY RADIOISOTOPE USE AT 57 V.A. HOSPITALS

Year	Gallium	Thallium
1976	3,700	203
1977	5,867	837
1978	7,970	1,495
1979	9,618	3,411
1980	11,375	4,312

Finally, from an industrial or commercial point of view, it would be important to know what is the current status and what are the recent developments in the thallium market. The best estimate I could find was a review by Richard B. Emmitt of Eberstadt & Co., a New York stock brokerage firm (Tables 8 & 9, from Diagnostic Imaging, June 1981).

Table 8 Thallium market projections ($ in millions)

	1978		1979		1980		1981*		1982*	
Manufacturer	**Sales**	**Share**	**Sales**	**Share**	**Sales**	**Share**	**Sales**	**Share**	**Sales**	**Share**
New England Nuclear	$ 7	88%	$ 14	82%	$ 20	71%	$ 22	59%	$ 22	51%
Mallinckrodt[1]	—	—	1	6%	4	14%	6	16%	8	19%
Medi-Physics[2]	1	13%	2	12%	4	14%	7	19%	9	21%
Other	—	—	—	—	—	—	2	5%	4	9%
Total	*$ 8*	*100%*	*$ 17*	*100%*	*$ 28*	*100%*	*$ 37*	*100%*	*$ 43*	*100%*

Table 9 Current and projected thallium capacity

Manufacturer	**System**	**Start-up date**	**NDA status**	**1980 sales***	**Annual Capacity* (doses 1983)[3]**
New England Nuclear	CS 30 Cyclotron (3)[1]	In production	Approved	$18 million	150,000
	LINAC	1981	Approved	—	400,000[3]
Mallinckrodt	Cyclotron (Petten, Holland)	In production[2]	Approved	*$ 3 million*	50,000[4]
	CS 30 Cyclotron	1981,[4,5]	Approved	—	50,000[4]
	CP 42 Cyclotron	1982	Approved	—	100,000
Medi-Physics (Hoffman-LaRoche)	CS 30 Cyclotron (Japan)	In production[2]	1981	$ 2 million	50,000[4]
	CS 30 Equivalent	1981	1981	—	25,000[4]
	Scanditronix #1	In production	1981	3 million[5]	100,000
	Scanditronix #2	1981	1981	—	100,000
Amersham	CP 42	1982	1982	—	100,000
RadPharm	CS 30	1981	Unknown	—	50,000
					1,175,000

Between 1977 and 1980, industry invested between $20 and 25 million for facilities to produce thallium, whose sales were expected to increase from $8 million in 1976 to $43 million in 1982. Approximately 180,000 thallium doses were delivered to patients in the United States during 1979, and 225,000 in 1980. U.S. industrial capacity is estimated to be one and a quarter million doses by 1983, while estimates of the annual growth rate over the next two to four years have been reduced from 50 percent to 25 percent. I believe this is based on the increased growth of gated wall motion studies and may not include consideration of the effect of the introduction of new cardiac radiopharmaceuticals labeled with ^{99m}Tc, ^{123}I, ^{75}Br, or some other radionuclide.

A word about the radiohalogens (Tables 10 & 11). It appears that, excluding ^{18}F, the most important radionuclides in this group will be ^{75}Br and ^{123}I. There is considerable difference of opinion as to the most cost-beneficial production method for ^{123}I. There is no doubt that radionuclidic and chemical contaminants interfere greatly with the labeling process and result in unnecessary additional radiation burden and image degradation.

The eventual utility of a radionuclide as a radiolabel is dependent on several factors, including the nuclear characteristics of physical half-life and nuclear decay scheme, specific activity, chemical purity, and radiochemical purity. It is beyond the scope of this presentation to discuss these features in detail, and it would be redundant since the desirability of maximizing all of the above are self-evident to all of the above participants. Yet the lack of enough of the "right kind" of ^{123}I remains an enigma. Clinical use of ^{123}I began in 1975, and use has apparently leveled off at about 25-30 percent of thyroid uptakes and scans performed in the U.S. (It is estimated that about 195,000 thyroid uptakes and 580,000 thyroid scans were performed in 1981 in patients referred to a hospital facility.) The routine clinical demands are probably exceeded only by the clinical research demands for more and better ^{123}I. The dosimetry of ^{123}I is summarized in Table 12.

The absorbed dose from the radiocontaminants may be equal to that from the ^{123}I itself. For example, if pure ^{123}I was available, one could give more isopropyl (^{123}I)p-iodoamphetamine than is now administered. Therefore, an increased number of photons would be available, the degraded images that result from the ^{124}I present would be improved, and the low photon problem now present in single photon emission computed tomography reconstruction would be reduced.

Despite the large accelerators present at Los Alamos, Brookhaven, and Fermi, the research laboratories have not been able to produce the quantities of ^{123}I desired by the biomedical community. Furthermore, there has been a decrease in the exploration of alternate production methods.

TABLE 10

PRODUCTION OF RELEVANT RADIOHALOGENS

Nuclide	Major Production Methods	Yield (mCi/μAh)	Particle Energy (MeV)
^{18}F	$^{16}O(^{3}He,p)^{18}F$	6	36 → 0
	$^{20}Ne(d,\alpha)^{18}F$	17	15 → 0
^{75}Br	$^{75}As(^{3}He,3n)^{75}Br$	5	36 → 30
^{77}Br	$^{75}As(\alpha,2n)^{77}Br$	0.41	28 → 14
	$^{79}Br(p,3n)^{77}Kr \xrightarrow{\beta^+} {}^{77}Br$	1.5	65 → 25
^{123}I	$^{124}Te(p,2n)^{123}I$	20	26 → 23
	$^{127}I(p,5n)^{123}Xe \xrightarrow{\beta^+;EC} {}^{123}I$	11	65 → 50

FROM STOCKLIN, COENEN

TABLE 11

PHYSICAL PROPERTIES AND CALCULATED MAXIMAL SPECIFIC ACTIVITIES OF SOME RADIOISOTOPES

Radio-Isotope	Physical Half-Life	Y-Energies KeV	Calc Max Spec Act kCi/mole*
Carbon-11	20 min	511	9,500
Bromine-75	95.5 min	511 286	1,960
Fluorine-18	110 min	511	1,700
Iodine-123	13.3 h	159	240
Bromine-82	35.5 hr	554 619 ++	88
Bromine-77	57 h	239 520	56
Iodine-131	8.1 d	364	16
Iodine-125	59.7 d	35	2.2

*X10^3

TABLE 12

COMPARATIVE RAD DOSE FOR THYROID STUDIES

	uCi Dose	Thyroid		Whole Body	
Tc-99m	10,000		5.0		.14
I-131	25		52.0		.009
I-123	*100*	*2.0*		*0.007*	
I-124	0.01	0.01		0.0002	
I-125	0.6	0.72	2.73	0.0023	.010
I-123	100				
I-124	1.0				
I-126	0.5				
I-130	3.0				
I-131	0.5		6.0		.028

Nuclear Oncology. Another specific example is found in nuclear medicine studies related to the diagnosis and management of patients with malignancy. In its 1982 "Cancer Facts & Figures," the American Cancer Society predicts that there will be 430,000 deaths from cancer this year in the United States, including 111,000 from lung cancer. The ACS also estimates that there will be 9,000 more cancer deaths this year than in 1981, and that there will be 129,000 new cases of lung cancer, 123,000 new cases of colon and rectal cancer, 112,000 new breast cancer cases, and 73,000 new patients with cancer of the prostate.

Despite these discouraging statistics, analyses of new epidemiologic data indicate that there has been a marked improvement in the survival rate and quality of life among Americans with cancer. Fourteen specific types of malignancy that had poor prognoses a few decades ago are now being cured in many cases, principally because of early aggressive chemotherapy. These include several different primary bone cancers of different endocrine tissues (choriocarcinoma, testicular, ovarian, and breast cancers). Clearly, some successes in the war on cancer have been achieved and the promise for more is great.

In the practice of nuclear medicine, the major emphasis has been transferred from therapy to the use of imaging tests which utilize newly developed radiopharmaceuticals. These techniques now permit early detection and staging, and have found particular use in monitoring therapeutic progress and in rapidly and relatively inexpensively evaluating specific complaints in patients who have had a malignancy. How important is it to determine the status of regional skeletal metabolism in a woman who develops pain in a bone following minimal trauma or no history of trauma, and who has had a malignant breast tumor removed? Very important, I would submit. Although the imaging procedures are unquestionably a valuable supplement to other tests and have found wide acceptance among oncologists, there is no question that the results of these procedures are relatively non-specific. Along with efforts to

develop circulating "tumor markers," nuclear medicine practitioners in collaboration with others are pursuing more specific radioactive tracers that will allow rapid determination of the proper course of therapy.

Bone scans, ^{67}Ga citrate scans, nuclear cardiology studies, and newer labeled antibodies or other protein receptor radiopharmaceuticals are helpful in the staging of disease, in monitoring the response to therapy, in detecting complications (such as the localization of an abscess or other complicating infection), and in evaluating drug toxicity affecting the heart or lungs.

Pediatric Nuclear Medicine. Nuclear medicine techniques have also improved health care and reduced costs in pediatric medicine. Several specific examples have already been mentioned. A bone scan has been found to be a most useful diagnostic technique for differentiating cellulitis from osteomyelitis at their early stages. Thus, the test allows a decision to be made between a short hospitalization for a child with cellulitis, as opposed to several weeks of hospitalization and extended drug therapy for a child with osteomyelitis. Bone scanning and kidney scanning are probably the two most frequently ordered nuclear medicine procedures in a pediatric hospital. Other uses include the differential diagnosis of a painful testicle (to differentiate an epididymitis from torsion, newer methods of cardiac diagnosis (including identification of many forms of correctable congenital heart disease), and management of malignancy.

Since all of the nuclear medicine tests can be readily performed in an outpatient setting, the ability to make an early diagnosis avoids the trauma of extensive diagnostic workup and unnecessary hospitalization. Another distinct advantage of all nuclear medicine tests is that they can be performed on patients who are allergic to radiographic contrast material.

Nuclear Neurology. Although transmission computerized tomography has generally replaced radionuclide brain scans for the diagnosis of central nervous system disease, several of the nuclear medicine tests still retain their usefulness in the diagnosis of selected diseases of the brain, such as normal pressure hydrocephalus in a patient with large ventricles, or the detection of an isodense subdural hematoma. However, newer techniques have opened exciting new vistas. Up to the present time, knowledge of the localization of cerebral function and hemisphere localization in man has been based almost entirely on inferences drawn from studying patients who had developed destructive lesions in the central nervous system. Newly developed techniques designed to measure regional cerebral blood flow and regional metabolism, however, mean that future studies will be limited only by the imagination of the investigators (Table 13). Although earlier studies used radiopharmaceuticals labeled with positron radionuclides, which require positron detection instrumentation and an on-site cyclotron facility, several groups of investigators are now examining radiopharmaceuticals labeled with single

gamma-emitting radionuclides. The ultimate success of this strategy will depend on the related development of appropriate instrumentation that will allow three-dimensional reconstruction of the spatial distribution of these single photon emitting radiopharmaceuticals. Validation of the single photon technique will allow widespread utilization of the fundamental techniques now being proposed and perfected. We are hopeful that receptor binding radiotracers, when properly radiolabeled, will also find wide use because of the elucidation of the role of receptors in a large number of specific biochemical reactions, in understanding neuropharmacology, and because of the changes in receptor number and receptor affinity described as a function of different disease processes.

TABLE 13

CLINICAL USES OF GAMMA-LABELED NEURORADIOPHARMACEUTICALS

1. Early diagnosis of dementia
2. Management of patients with epilepsy
   identify focus, selection for surgery
3. Studies to limit cerebral ischemia
4. Evaluate chemotherapy of tumors
5. Label drugs to follow brain localization precisely
6. Quantify discriminate functions
   speech, language, praxis, visual, motor, and
   sensory functions
7. Classify mental retardation
8. Reclassify "mental illness"
9. Record natural history
10. Identify organic changes in "the crock" patient

It has been pointed out that up to the present time the practice of medicine has relied almost exclusively on the knowledge learned in pathology, supplemented by knowledge obtained from physiological experiments involving animals. To quote Dr. Henry Wagner, "We are beginning to be able to view the structure and function of the human body noninvasively, and even exceed the perception of the pathologists at the autopsy table or the surgeon at the operating table. We are progressively improving our means of processing the dynamic state of body constituents. These new techniques permit us to view our patients' bodies as a symphony of processes, not as simply static structures. Measurements of temporal changes and patterns--the very essence of human physiology--are becoming commonplace."

Is nuclear medicine a clinical specialty? Review of the numbers of papers submitted to the 1982 Annual SNM meeting will answer that question adequately (Table 14). The total number of papers submitted continues to increase each year, so that even with an expanded program it has not been possible to present more than 50 percent of the total.

TABLE 14

ABSTRACTS SUBMITTED FOR 1982 ANNUAL MEETING

Instrumentation		59
Computers and Data Analysis		78
Radioassay		29
Radiohalogenated Radiopharmaceuticals		32
Radiopharmaceutical Chemistry - General		32
Radiopharmaceutical Chemistry Sciences		22
Short-lived Radiopharmaceuticals		23
Dosimetry/Radiobiology		21
Clinical:		535
Bone/Joint	37	
Cardiovascular - Basic	50	
Cardiovascular - Clinical	161	
Correlation of Imaging Modalities	12	
Endocrine	23	
Gastroenterology	51	
Hematology	21	
Infectious Disease and Immunology	16	
Neurology	36	
Oncology	31	
Pediatrics	18	
Peripheral Vascular	10	
Pulmonary	39	
Renal/Electrolyte/Hypertension	30	
SUBTOTAL		831
Less abstracts jointly reviewed in two categories		-9
TOTAL		822

Other useful tables, suitable labeled, have also been included (see Tables 15-19).

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TABLE 15

CLINICALLY USED RADIONUCLIDES

YEARS	RADIONUCLIDES
1920-1930:	Radium-C
1930-1950:	P-32; I-131; Na-24; Co-60
1950-1964	H-3; C-14; Cr-51; Fe-59; Co-57; Se-75; Sr-85, 87m; In-113m; I-125; Yb-169; Hg-197, 203; Au-198
1964-1972:	F-18; Ga-67; Tc-99m; In-111; I-123; Xe-127, 133
1972-1980:	Tl-201; C-11; N-15; O-15
Enriched Targets:	Ga-67; Tc-99m; In-111; I-123; Tl-201

TABLE 16

CHEMICAL CLASSIFICATION OF RADIONUCLIDES FOR IN-VIVO STUDIES IN NUCLEAR MEDICINE AND LIFE SCIENCES

(modified from Stöcklin)

1. "Organic" Short-lived B^+ emitters
   (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{30}P etc.)
2. Halogens and Rare Gases
   (^{34m}Cl, $^{75,76,77}Br$, ^{123}I, ^{79}Kr, ^{81m}Kr, ^{125}Xe etc.)
3. Generator Isotopes
   (^{68}Ge-^{68}Ga, ^{81}Rg-^{81m}Kr, ^{82}Sr-^{82}Rb, ^{99}Mo-^{99m}Tc, ^{113}Sn-^{113}In, ^{191}Os-^{191m}Ir etc.)
4. Alkali and Alkali Like Metals
   (^{43}K, ^{81}Rb, ^{129}Cs, ^{201}Tl etc.)
5. "Inorganic" Radionuclides
   (^{28}Mg, ^{47}Ca, ^{48}Cr, ^{67}Ga, $^{73,75}Se$, ^{85}Sr, ^{97}Ru, ^{111}In, ^{97}Hg)

TABLE 17

ALKALI AND ALKALI-LIKE METALS

Radio-isotope	Half-life	Major Production Methods	Energy (MeV)
^{38}K*	7.7 min	$^{35}Cl(\alpha,n)^{38}K$	15 → 6
		$^{38}Ar(p,n)^{38}K$	
		$^{40}Ar(p,3n)^{38}K$	33 → 30
		$^{37}Cl(^{3}He,2n)^{38}K$	
		$^{37}Cl(\alpha,3n)^{38}K$	
^{43}K	22.2 h	$^{40}Ar(\alpha,p)^{43}K$	35 → 15
		$^{43}Ca(n,p)^{43}K$	fission spectrum
		$^{nat}Ti(d,x)^{43}K$	85 → 50
^{81}Rb*	4.6 h	$^{79}Br(\alpha,2n)^{81}Rb$	20 → 10
		$^{81}Br(\alpha,4n)^{81}Rb$	
		$^{80}Kr(^{3}He,pn)^{81}Rb$	
		$^{80}Kr(d,n)^{81}Rb$	
		$^{nat}Kr(p,xn)^{81}Rb$	
^{127}Cs	6.2 h	$^{127}I(\alpha,4n)^{127}Cs$	150 → 40
^{129}Cs	32.1 h	$^{127}I(\alpha,2n)^{129}Cs$	150 → 20
		$^{133}Cs(p,5n)^{129}Ba$	
		$(\beta^{+}, EC)^{129}Cs$	
^{201}Tl	73.5 h	$^{nat}Tl(p,xn)^{201}Pb$	45 → 20
		$(EC)^{201}Tl$	
		$^{nat}Hg(p,xn)^{201}Tl$	20 → 0
		$^{nat}Hg(d,xn)^{201}Tl$	15 → 0
		$^{209}Bi(p,spallation)$	800 MeV

*β^{+} emitting nuclide

FROM STOCKLIN & COENEN

TABLE 18

CYCLOTRON PRODUCED
RADIONUCLIDE GENERATORS

Generator	Daughter $T_{1/2}$	Parent $T_{1/2}$	Production Reactions
^{52}Fe-^{52m}Mn*	21 min	8.2 h	$^{50}Cr(\alpha,2n)^{52}Fe$ $^{50}Cr(^{3}He,n)^{52}Fe$ $Cr(\alpha,xn)Fe$ *Spallation*
^{68}Ge-^{68}Ga*	68 min	287 d	$^{66}Zn(\alpha,2n)^{68}Ge$ $^{68}Zn(\alpha,4n)^{68}Ge$ $^{69}Ga(p,2n)^{68}Ge$ $^{71}Ga(p,4n)^{68}Ge$
^{81}Rb-^{81m}Kr	13 sec	4.6 h	$^{79}Br(\alpha,2n)^{81}Rb$ $^{81}Br(\alpha,4n)^{81}Rb$ $^{80}Kr(^{3}He,pn)^{81}Rb$ $^{80}Kr(d,n)^{81}Rb$ $^{nat}Kr(p,xn)^{81}Rb$ $^{85}Rb(p,5n)^{81}Sr \xrightarrow{\beta^+} {}^{81}Rb$
^{82}Sr-^{82}Rb*	1.3 min	25 d	$^{85}Rb(p,4n)^{82}Sr$
^{87}Y-^{87m}Sr	2.8 h	3.3 d	$^{86}Sr(d,n)^{87}Y$ $^{87}Sr(p,n)^{87}Y$ $^{88}Sr(p,2n)^{87}Y$
^{128}Ba-^{128}Cs*	3.8 min	2.43 d	$^{133}Cs(p,6n)^{128}Ba$ $^{133}Cs(d,7n)^{128}Ba$

*β^+ emitting nuclide
FROM STOCKLIN & COENEN

TABLE 19

SOME OTHER CYCLOTRON-PRODUCED METAL ION RADIONUCLIDES

Radio-isotope	Half-life	Major Production methods	Energy (MeV)	Application
^{28}Mg	21.1 h	$^{26}Mg(t,p)^{28}Mg$	4→0	Mg-deficiency studies
		$^{26}Mg(\alpha,2p)^{28}Mg$	140→20	
		$^{27}Al(\alpha,3p)^{28}Mg$	140→30	
^{48}Cr	23 h	$^{nat}Ti(^{3}He,xn)^{48}Cr$	140→30	Labeling of blood cells
		$^{nat}Ti(\alpha,xn)^{48}Cr$	140→30	
^{51}Cr	27,7 d	$^{51}V(p,n)^{51}Cr$	30→5	
		$^{51}V(d,2n)^{51}Cr$	30→5	
^{52}Fe*	8,2 h	$^{50}Cr(\alpha,2n)^{52}Fe$	30→10	Blood cell labeling iron metabolism
		$^{50}Cr(^{3}He,n)^{52}Fe$	20→5	
^{55}Co*	18 h	$^{56}Fe(p,2n)^{55}Co$	40→15	
^{57}Co	270 d	$^{56}Fe(d,n)^{57}Co$	20→5	Tumor seeking complexities
^{67}Ga	78,3	$^{65}Cu(\alpha,2n)^{67}Ga$	30→10	
		$^{66}Zn(d,n)^{67}Ga$	20→0	
		$^{68}Zn(p,2n)^{67}Ga$	30→15	
^{111}In	2,8 d	$^{109}Ag(\alpha,2n)^{111}In$	30→10	
		$^{111}Cd(p,n)^{111}In$	20→5	
		$^{nat}Cd(d,xn)^{111}In$	30→0	

FROM STOCKLIN & COENEN

APPENDIX 9

Isotope Separation by Gaseous and Liquid Thermal Diffusion and by Chemical Exchange

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Stable isotopes are separated on a commercial scale for the U.S. Department of Energy at three locations, MRC-Mound, Los Alamos, and Oak Ridge. Each of the laboratories has its own areas of specialization in isotope separation, and these separation facilities are generally complementary to each other.

Oak Ridge has used the Calutrons (mass spectrometry) since the 1940's. The principal advantage of the Calutron is its ability to separate the isotopes of a very broad spectrum of elements and to relatively quickly change from one element to another. This ability is unmatched by any of the other isotope separation methods, or indeed by any combination of the other separation methods; hence, the Calutrons are truly a national resource.

The efficiency of the Calutron is low and the cost of separation is high, especially if two enrichment steps are required to achieve the desired concentration. Furthermore, the separation cost per gram of isotope is relatively independent of the quantity separated. Hence, this technique is best suited to separating small quantities of isotopes; e.g., less than 10 grams per year.

Los Alamos uses cryogenic distillation to separate the isotopes of carbon, oxygen, and nitrogen (ICON's). This is a highly efficient and relatively simple procedure, but it is limited to elements which are volatile or have volatile compounds (e.g., CO) at reasonably accessible temperatures. Because of relatively high capital costs, the unit separation cost by cryogenic distillation decreases substantially as the separated quantity increases. With the current facility, the optimum separation rate is in the range of 10^4 grams per year. The isotopes separated at Los Alamos are transferred to MRC-Mound for sale.

MRC-Mound separates isotopes by gaseous thermal diffusion, liquid thermal diffusion, and by chemical exchange.

Gaseous thermal diffusion is now used only to separate noble gas isotopes and deuterium, having been supplanted by distillation in the case of the ICON's. Liquid thermal diffusion (LTD) is currently used in the separation of chlorine, bromine, and sulfur isotopes. LTD requires a stable liquid form (e.g., CS_2) in the temperature range from 0-300°C. It is expected that there are several metals which have compounds that will be separable by liquid thermal diffusion, but work on this is in its early stages. For example, basic properties measurements on methyl zinc have indicated that this may be an acceptable separation medium for zinc. The unit cost of separation by thermal diffusion is relatively independent of volume above a rate of 10-100 grams per year; hence, in the 10^2 gram per year range LTD may be preferable to the Calutrons.

Chemical exchange isotope separation requires the existence of two immiscible chemical forms of the element to be separated, at least one of which must be fluid. Preliminary work has been done on separating calcium and sulfur by chemical exchange. Many other elements are potentially separable by chemical exchange, and Mound is currently investigating the potential of chemical exchange to separating a number of metal isotopes. Capital costs are substantial, but overall efficiency is high, thus economics of scale may be important. Chemical exchange is best suited to separation of annual quantities of 100g or more, but for those cases where it is applicable, reductions of 90%, 99%, or more from Calutron separation costs are possible.

Chemical exchange and liquid thermal diffusion both have attributes which prevent their replacing the Calutrons as a general isotope separation method. Each requires quantities of material which exceed by far the most liberally estimated requirements for many isotopes. Each requires a unique chemical system for each element separated. Both are at a disadvantage at separating middle isotopes; e.g., calcium-44. Consider, for example, neodymium-146, a middle isotope with projected requirements of only 330 mg.[+] At the current price of $1.30/mg, this has a value of less than $500. It is inconceivable that any amount of neodymium-146 could be separated for $500 by chemical exchange or thermal diffusion, yet this can be done with the Calutron.

Where larger quantities are involved, however, chemical exchange, liquid thermal diffusion, or other advanced processes should be used whenever possible. Whereas separation of 100 grams of calcium-48 by chemical exchange may require a few weeks to a few months depending upon the size of the separation system, this separation would require about two years using the entire currently operating Calutron capacity*, and would preclude separation of any of the remaining 240 stable isotopes for that time.

One final point should be made. Mound is the only DOE laboratory actively pursuing development of commercial-scale isotope separation. In contrast to the Calutrons, the separation of a new element by liquid thermal diffusion or chemical exchange requires a long development period. At our current level of understanding, a new separation takes from two to five years to develop to the point where it is in regular production. In the future, new separations may be added more rapidly, but today it is very important to know as early as possible about potential needs for separated isotopes so that Mound can work together with the isotope users to establish the new product. This workshop is an important step toward maintaining and improving a valuable national resource, i.e., a U.S. source of separated stable isotopes able to supply both the variety and quantity of stable isotopes required by the research, biomedical, and commercial markets.

[+] Dr. Michael Zisman, this conference.
* Calculated using 0.1 mol/day of calcium per section.

APPENDIX 10

LASER ISOTOPE SEPARATION - AN ALTERNATIVE PRODUCTION METHOD

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At present, less than five elements account for 70% to 80% of the demand for stable isotopes. This unbalanced demand severely limits the availability of the Calutrons at Oak Ridge for the task to which they are best suited, namely, the production of a wide variety of isotopes for research purposes. The Workshop therefore adopted a recommendation calling for greater efforts to develop alternative separation methods as a supplement.

The atomic vapor laser isotope separation (LIS) process[1] is an ideal supplementary alternative, since it offers the potential for rapid low-cost production of significant greater quantities of the isotopes in primary demand, mostly metals with mass numbers above 100. Fortunately, much of the R & D work on a process for separating uranium[2,3] is also applicable to the separation of the isotopes of such elements as thallium, cadmium, osmium, tellurium, indium, and lead. These elements have qualitative similarities that would allow the development of a cost-effective laser process that could be used to produce isotopes of a number of elements without major hardware changes. Recently, our company has directed its attention towards developing such a process for the separation of thallium. We believe it may now be possible to supply a significant fraction of the current national need for thallium by undertaking a two to three year effort that would involve spending about $1 million for R&D and perhaps $2 million for construction of a pilot plant.

The first phase of such a program would involve the determination of key physical parameters for thallium and several other elements, identification of the optimum laser system and separation scheme, and a proof-of-principle experiment. The second phase would involve construction of a pilot plant, which could be expanded at modest cost through the acquisition of additional laser capability. The initial operating costs of such a pilot plant appear to be competitive with the costs of operating the Calutrons at Oak Ridge, while an expanded plant would have the potential to reduce operating costs per unit of production by perhaps ten-fold.

The basic steps in the atomic vapor laser isotope separation process, as invented at the Avco Everett Research Laboratory in 1969[1] and developed under the auspices of Jersey Nuclear-Avco Isotopes, Inc. (JNAI)[3], are:

i. vaporization of the source material;

ii. selective photo-ionization of the desired isotopic species; and

iii. selective extraction and collection of photo-produced ions.

We have investigated the vaporization of heavy metallic elements rather thoroughly and we have this part of the process well in hand on the scale necessary for this application. We first demonstrated selective photo-ionization of uranium[2] in 1971, and several color schemes for selective photo-ionization of thallium have already been identified in our laboratory. In addition to work on other elements, further work would also be required to optimize these color schemes and the choice of lasers. However, these choices are somewhat flexible because the photo-ionization cross sections, and the unit values of the end products are much greater for these elements than they are for uranium. Although the extraction and collection of ions is difficult, we have a great deal of proprietary expertise in this part of the process as a consequence of our work on uranium[1,2,3] and have identified a workable scheme.

Since the requisite facilities and personnel are already in place, work on such a program could begin on short notice with relatively modest equipment and instrumentation costs. Because the demand for stable isotopes of elements other than uranium are modest, the creation of a pilot plant would only involve a single stage of scale-up beyond the existing research facility. Such a plant could be adapted to the enrichment of isotopes other than those of thallium at acceptable cost if advance planning and R&D were undertaken to provide the requisite flexibility. The LIS process would be particularly advantageous for the isolation of rare isotopic species with neighbors on both sides, because photons are highly selective and also because the photon requirements and space charge limitations are proportional to the mass of the desired product stream rather than to the mass of the feed stream.

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2. G. S. Janes, et al., "Two-Photon Laser Isotope Separation of Atomic Uranium - Spectroscopic Studies, Excited State Lifetimes, and Photoionization Cross Sections", IEEE JQE 12, No. 2 (1976).

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APPENDIX 11

The Vacuum Arc Centrifuge

M. Krishnan and J. L. Hirshfield

I. INTRODUCTION

The separation of elements and isotopes by means of rotating magnetized plasma columns has been under study for the past two years at Yale. The instrument used in these studies is a laser-triggered vacuum arc centrifuge. Unlike its partially ionized gaseous predecessors, this vacuum arc centrifuge is sustained by the erosion and ionization of the cathode material, thus producing relatively pure, highly ionized, rotating plasma columns of the cathode material. Any solid metal, or mixture of metals, can be converted into plasma, and the constituent isotopes partially separated in the centrifuge, by fabricating the arc cathode out of the desired metals. The device also offers the possibility of operation with non-conducting solid elements or compounds by imbedding the desired substance in a conducting matrix.

A wide variety of metals and combinations of metals have been studied so far, ranging from C through Cu to Cd/Sn. Typical angular rotation frequencies $\sim 10^5$ rad/sec have been measured, with concomitant enrichments up to a factor of two for ^{65}Cu.

The device in its present form is not a viable source of partially enriched stable isotopes at a competitive cost. Nevertheless, reasonable estimates of the future capability and cost of a larger version of the device can be made. It should be emphasized that a concerted research and development effort would be a necessary prerequisite to making the device a practical isotope separator.

II. DESCRIPTION OF THE VACUUM ARC CENTRIFUGE

Details of the operation of the vacuum arc centrifuge are given in M. Krishnan et al.[1] The salient features are reviewed briefly here. Figure 1 is a schematic drawing of the centrifuge. The cathode is on axis, at the upstream end of a grounded vacuum vessel 1.5 m long which serves as the anode. The laser pulse delivers a few joules of energy to the cathode face, thus producing a transient laser plasma and triggering the vacuum arc. Several kilojoules of capacitively stored energy are thus delivered to the vacuum arc, resulting in a several kiloampere peak current discharge of millisecond duration. The cathode material is ionized at a rate of roughly 2×10^{-4} g per coulomb of charge transferred across the discharge. The ionized plasma is collimated and confined by the axial magnetic field at field strengths up to 0.4 T. The radial component of the self-consistent electric field in the plasma, along with the axial magnetic field, causes the column to rotate as a rigid rotor for carefully chosen configurations of electrode geometry, arc current, and guide magnetic field.

Pure columns of carbon, copper, and zirconium, as well as mixtures of such metals as aluminum/titanium, copper/nickel, and cadmium/tin have been observed to rotate in this device, with typical angular rotation frequencies $\sim 10^5$ rad/sec. Concomitant with such rotation, radial separation between elements, or isotopes of the same element, has also been measured--for example, Cu/Ni. At a distance of 1 m downstream from the cathode, the collected material in an annulus containing 15 percent of the total flux was found to contain a 50 percent higher abundance[2] of the

heavier element, Cu, than the core. Time-resolved measurements of the separation between isotopes of Cu in a pure Cu plasma revealed that ^{65}Cu was enriched[3] by up to 100 percent at certain times during discharge. While the partial separations between elements or isotopes in a single pass through the centrifuge are low compared with the enrichments achieved by Calutrons, the throughput is relatively high. The flux of ions in the centrifuge is equivalent to ion currents $\sim$100 A. If such an arc were operated continuously, and only 1 percent of the plasma stream was collected as a useful product of desired enrichment, the resulting net beam current of 1 A would still compare favorably with the 25-50 mA currents typical of Calutrons.

It appears likely that an increase in plasma column diameter and longer column length (allowing more rotation orbits for a streaming ion) could lead to higher enrichments at correspondingly higher cuts. Since, to lowest order, the $\overline{E} \times \overline{B}$ rotation of the Column is weakly sensitive to ion mass and charge, it is conceivable that stable isotopes of higher mass, such as ^{203}Tl, could also be centrifugally enriched.

III. PRACTICAL CONSIDERATIONS

A distinguishing feature of the vacuum arc centrifuge is its demonstrated potential for high throughput, even though the enrichments achieved are relatively low compared to those of Calutrons.

Let us assume that such an arc were operated in a repetitively pulse mode with a 10 percent duty factor. The average arc power required would then be $\sim$ 50 kW, a figure well within the realm of present-day arch discharge technology. Such a power level would correspond to average arc currents $\sim$ 500 A, which in turn suggests that target material could be converted from solid to plasma at a rate of $\sim$ 100 mg/sec, or $\sim$ 13 mol/day of Cu. If only 1 percent of this flux achieved the desired enrichment, the net throughput of $\sim$ 1 mol/day would be an order of magnitude higher than that for Calutrons, which is 0.1 mol of an element per operational day.[4] Such high fluxes are possible in the vacuum arc centrifuge because the plasma stream is quasi-neutral, whereas Calutrons operate with space-charge limited ion beams.

Any attempt to make detailed cost estimates of such a scheme at this time would be premature, since a pilot plant would have to be built and operated before reliable estimates of cost could be made. For the purpose of making a preliminary estimate, however, we consider here a scaled version of the vacuum arc centrifuge with two differences from the present version: replacement of the solid cathode by a ring cathode, providing a higher flux in the column at larger radii, where centrifugal separation is more effective, and an increase in plasma column length from the present 1 m to 3 m, allowing for multi-stage operation in one pass. As an example, a single-pass four-stage separator could be built by placing four annular collectors spaced 0.75 m apart along the column. Each collector would collect a given fraction of the flux, after which the transmitted plasma, continuing to rotate, would stream toward the next collector, diffusively expanding across the magnetic field to the same diameter as in the previous stage, thus achieving the same degree of separation.

Consider thallium to be the feed material. If each stage of the four-stage separator allowed 40 percent of the total flux in the column to be collected with a 40 percent increase in abundance of the heavier isotope, ^{205}Tl, the material in the residual core after four identical stages would contain 13 percent of the original feed, with an 80 percent abundance of ^{203}Tl. That is, one pass through the machine would enrich ^{203}Tl from 29.5 percent natural abundance to 80 percent abundance, with a net throughput of

about 5 mol/day if the arc were repetitively pulsed, with a 10 percent duty factor and 50 kW average discharge power. If the desired isotope is the heavier species, the same single-pass multi-stage concept would apply, but the material collected at each stage would impinge upon a solid disc in the core of the plasma column while allowing the annular plasma, enriched in the desired species, to continue rotation and further separation.

The separation of ^{48}Ca could be one application of this scheme, although the process would be complicated by the presence of six stable isotopes in the column. Furthermore, because of the low natural abundance of ^{48}Ca, the net throughput would be much lower than with thallium, corresponding under similar conditions to roughly 10^{-2} mol/day. To put the assumptions of 40 percent cut with 40 percent enrichment in some perspective, we have demonstrated that ^{65}Cu is enriched by 40 percent over ^{63}Cu in an annulus containing 20 percent of the total flux. An optimal version of the present device would therefore have to provide about twice as much separated flux as the present device. As stated earlier, operation with an annular cathode geometry in a larger plasma column might allow this goal to be achieved, provided the column rotated at similar frequency.

We turn now to the task of making rather crude estimates of the throughput capability and costs of a hypothetical pilot plant with a five-year amortization period. We assume here that the confining magnetic field would be produced by a 3 m long, 0.2 m bore super-conducting solenoid. A conventional magnet would require electrical power greatly in excess of the vacuum arc discharge power and would present a significant cooling problem. We therefore restrict our attention to the two proto-type separation schemes described above, one yielding 80 percent enriched ^{203}Tl with a $\sim$10 percent cut, the other yielding 50-80 percent enrichment ^{48}Ca with a 10^{-2} percent cut:

SINGLE-PASS, FOUR-STAGE VACUUM ARC CENTRIFUGE

THROUGHPUT CAPABILITY AND COSTS:

ionization rate of feed		2×10^{-4} g/c
average discharge current		500 A
plasma production rate		0.1 g/s
desired product yield:		
^{203}Tl (10 percent cut)		36 g/hr
^{48}Ca (10^{-2} percent cut)		0.036 g/hr
arc discharge average power		50 kW
vacuum system power		25 kW
superconducting magnet		5 kW
other power requirements		20 kW
TOTAL POWER COST @ \$0.04/kWh		\$3.60/hr
CAPITAL COSTS*		1.4 million
CAPITAL COSTS amortized over 5 years		\$32/hr
labor cost (skilled maintenance		\$40/hr
hidden costs		\$10/hr
	TOTAL COSTS	\$85.60/hr
COST OF PRODUCTS:		
^{203}Tl		\$ 2.40/g
^{48}CA		\$2,380/g

*This figure includes a 3 m long, 0.2 m bore superconducting solenoid system, vacuum vessel and pumps, target cooling system and target handling, power conditioning to obtain repetively pulsed power from the mains, collector assemblies, on-line mass spectrometers, and a microprocessor control system.

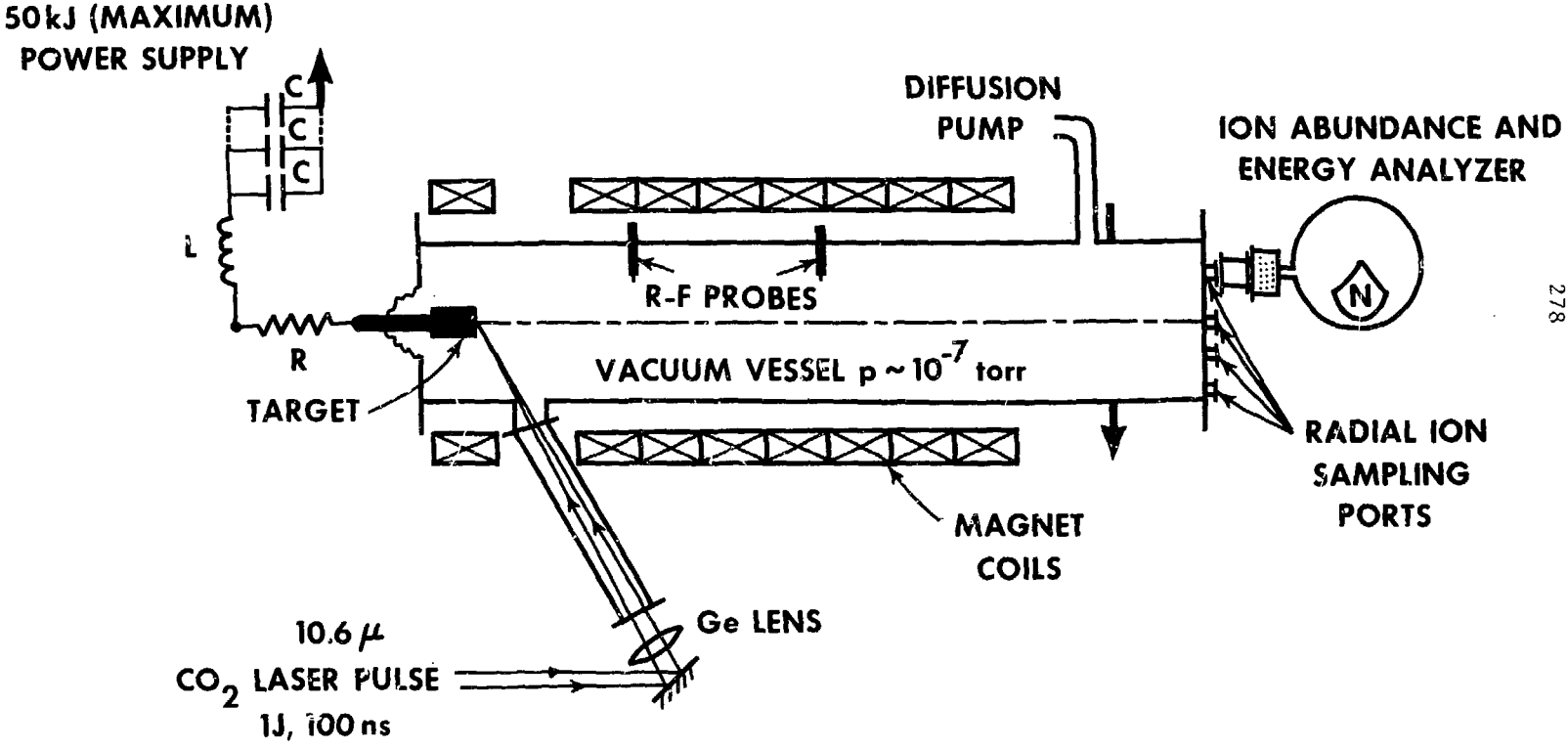

FIGURE 1. Schematic drawing of the vacuum arc centrifuge.

IV. CONCLUSIONS

The production costs estimated above for a demonstration pilot plant are well below the present market values of ^{203}Tl and ^{48}Ca. Given the high throughput capability ($\sim$ 1g ^{48}Ca/day), this scheme appears to merit further development. A note of caution is called for, however. A concerted development effort would be necessary before the pilot plant outlined above could be realized. The scaling physics learned along the way would in all likelihood alter--perhaps significantly--the cost and throughput estimates offered here. The numbers themselves are not as significant as the fact that in magnitude they appear to be a factor of 500 lower (in the case of ^{203}Tl) and 50 lower (in the case of ^{48}Ca) than the present market values of these products. Even if the eventual cost of stable isotopes enriched by this scheme were an order of magnitude higher than these estimates, such as a scheme would still seem to be feasible.

In summary, we reiterate that the vacuum arc centrifuge described here would allow operation with a wide variety of elements, offer potentially high throughput, and, if developed successfully, could yield single-pass enrichments at competitive cost. In an era of dwindling inventories and aging equipment, it would seem prudent to explore promising alternative separation schemes in order to achieve the goal of a more reliable supply of stable isotopes.

V. REFERENCES

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$$\frac{[^{65}Cu/^{63}Cu]_{\text{plasma}} - [^{65}Cu/^{63}Cu]_{\text{natural}}}{[^{65}Cu/^{63}Cu]_{\text{natural}}} \times 100\%$$
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