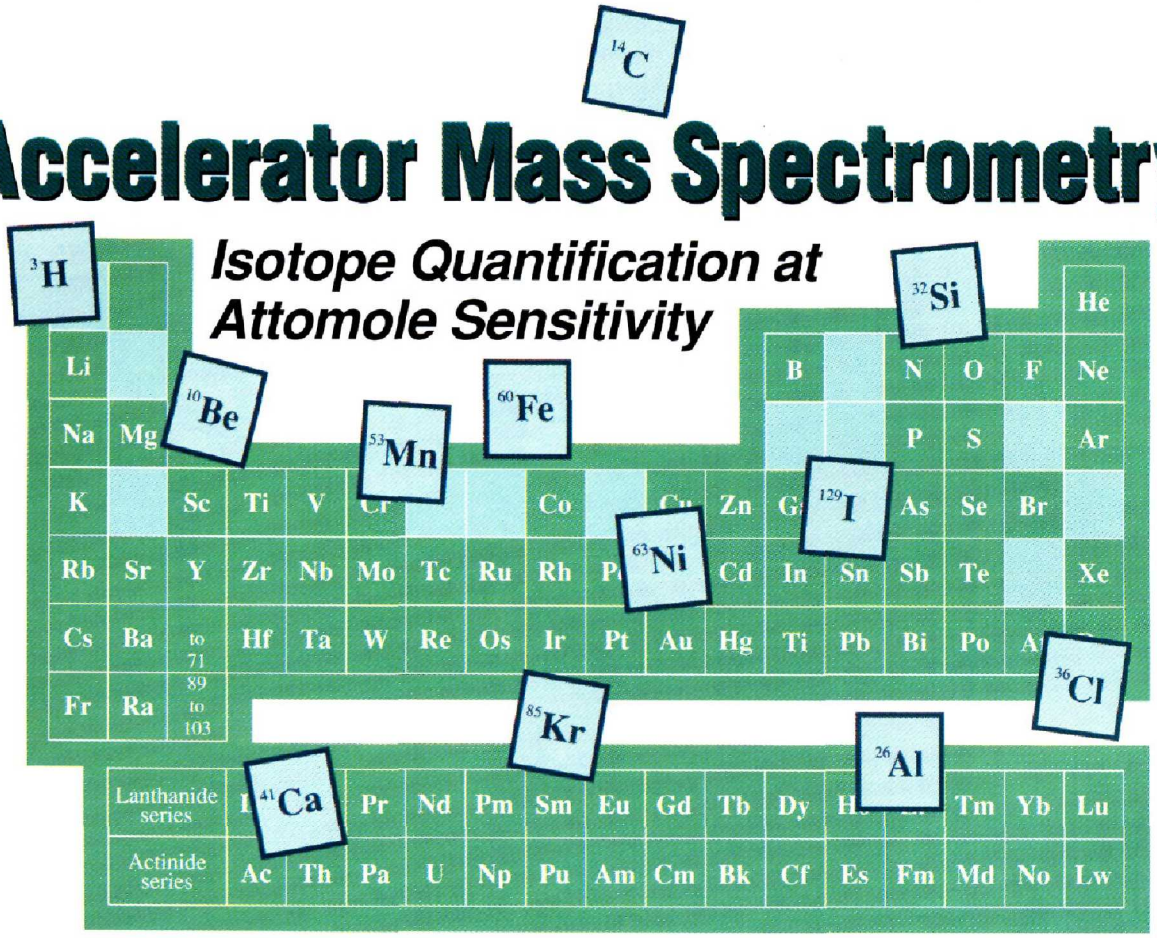
Accelerator Mass Spectrometry

Isotope Quantification at Attomole Sensitivity



Isotopic signatures contain information about a sample's molecular history and can be used to decipher mechanisms of chemical change. Natural and artificially enhanced isotopic concentrations of elements ranging from ^{3}H to ^{238}U are used in fields as diverse as the earth sciences, the life sciences, and archaeology to study chemical and physical pathways. For example, the stable isotopes of carbon and nitrogen can be used to study the photosynthetic pathway of plants, the dietary preferences of animals feeding on plants, or the balance of marine and terrestrial nutrition in a human population.

AMS can detect long-lived isotopes in extremely small samples

The concentration of ^{14}C, the longest lived radioisotope of carbon, records the time since the last carbon exchange with the atmosphere, providing information such as the age of an archaeological artifact or about the circulation of the world's oceans. In such studies, isotopic measurements must be made on materials of well-defined physical and chemical nature. This definition is often gained at the expense of sample size, creating a need for highly sensitive isotope detection techniques.

Methods of isotope quantification include MS for stable or long-lived isotopes and decay counting for radioisotopes. For short-lived radioisotopes (where the half life is less than a few years), decay measurements are efficient if performed for an appreciable fraction of the mean life or if the sample is large enough to provide statistically significant numbers of decays. For isotopes with long mean lives, however, these conditions are seldom met. For example, < 0.012% of a radiocarbon sample with a mean life of 8340 years decays in one year, and only 0.007% of ^{26}Al (with a mean life of 1.04 million years) decays in a person's 70-year life span.

MS can be used to efficiently determine isotope ratios (the concentration of rare isotope to the concentration of total element) as low as 10^{-9} in microgram to nanogram samples, but because natural abundances of isotopes with mean lives from tens to millions of years are 10^{-9} to 10^{-15} times elemental abundances, these isotopes cannot be detected efficiently by either "conventional" isotope ratio MS

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0003-2700/95/0367-353A/$09.00/0

(IRMS) or by decay counting. Accelerator MS (AMS), on the other hand, can be used for efficient detection of long-lived isotopes at part-per-quadrillion sensitivities with good precision.

In this article, we present an overview of AMS and its recent use in archaeology, geochemistry, and biomolecular tracing. More detailed discussions about the various methods used in AMS, types of instruments, and applications can be found in recent proceedings of AMS and radiocarbon conferences (*1–4*).

Development of AMS

Measurement of isotope ratios at the part-per-trillion level was attempted unsuccessfully in the mid-1970s by Anbar, who used tandem MS (*5*), and successfully by Muller, who used cyclotron MS (*6*). Other foundations of AMS arose in the 1960s and 1970s from physicists' efforts to produce energetic ion beams of elements heavier than helium for nuclear collision studies. Several factors, including the use of the cesium-sputter ion source, contributed to the development of practical AMS (*7*). Finally, two groups from nuclear accelerator laboratories barely 100 miles apart simultaneously published their methods of detecting natural ^{14}C at part-per-trillion levels using tandem Van de Graaff accelerators (*8*, *9*).

In the following decade, several accelerators were modified for part-time use as isotope detection systems. Dedicated AMS laboratories, primarily for ^{14}C dating, were based on new, 1.5–3 MV accelerators. Several laboratories refurbished higher voltage (5–10 MV) accelerators to study a wide range of isotopes. All of the approximately 40 AMS systems throughout the world now use various tandem electrostatic accelerators, although two groups are attempting to build small cyclotrons as "tabletop" systems (*10*, *11*).

MS at MeV energies

AMS uses a tandem mass spectrometer in which a dissociating gas or solid is placed in the evacuated ion path at high positive potential (1–25 MV) between a low-energy (20–100 keV/ion) mass spectrometer for negative ions and a high-energy (5–150 MeV/ion) momentum/charge spectrometry system for positive ions. Figure 1 and the accompanying photo show the Lawrence Livermore National Laboratory's AMS facility constructed between 1986 and 1989 from a used 10-MV tandem Van de Graaff accelerator. Other AMS facilities are similar in principle but differ in size, ion source, ion optics, accelerating voltages, particle-filtering elements, and final ion counters.

All AMS systems use cesium-sputter ion sources to produce negative ions from a small button of a solid sample containing the element of interest, such as graphite (C), metal halide (AgCl, AgI, CaF_2), or metal oxide (BeO, Al_2O_3), often mixed with a metal powder as binder and thermal conductor. The samples are bombarded by 3–10 keV Cs ions that physically knock atoms and molecules out of the sample and contribute an electron to a fraction of the ejected particles, forming negative elemental or molecular ions (e.g., BeO^-, C^-, CaF_3^-). Ions are selected at single atomic mass units through a magnetic dipole by switching the electrostatic potential on the magnet's vacuum chamber.

This low-energy spectrometer cannot resolve the small mass differences among the rare isotope and the nuclear or molecular isobars (e.g., ^{36}Cl, ^{36}S, and $H^{35}Cl$). A tandem electrostatic accelerator provides resolution of these interferences in two ways: Molecular isobars are removed by charge change from negative to multiply-positive ions in the dissociation cell within the high-voltage terminal of the accelerator; and nuclear ions—even isobars—can be uniquely identified using simple counting detectors, but only at the high ion energies (> MeV) that can be reached through accelerators.

The negative ions accelerate toward the positive terminal of the accelerator. They pass through a thin carbon foil or a localized gas that removes electrons from the ion through collisions with the electrons in the stationary foil or gas, making positive ions. From the positive terminal, ions of all elements in the incident beam are accelerated back to ground potential, attaining energies from a few MeV to more than 100 MeV, depending on their charge state and the accelerator voltage.

The number of electrons removed increases with ion velocity, and light ions attracted to the high-voltage terminal convert more readily to high positive-charge states. With a 7-MV terminal, the charge on most C^- ions changes to 4+, but Be ions that enter as BeO^- have maximum inten-

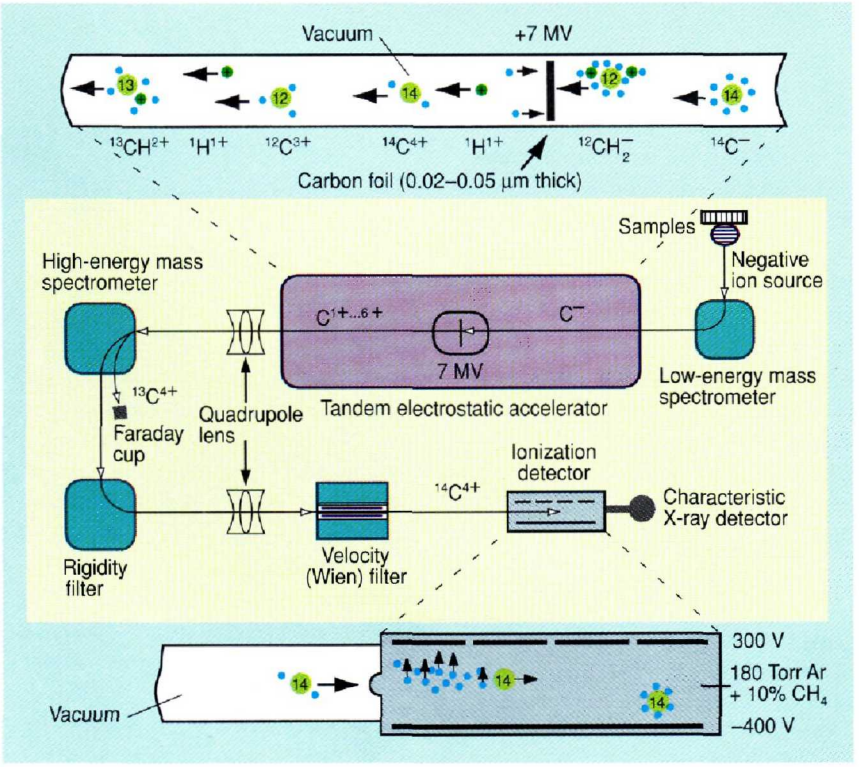
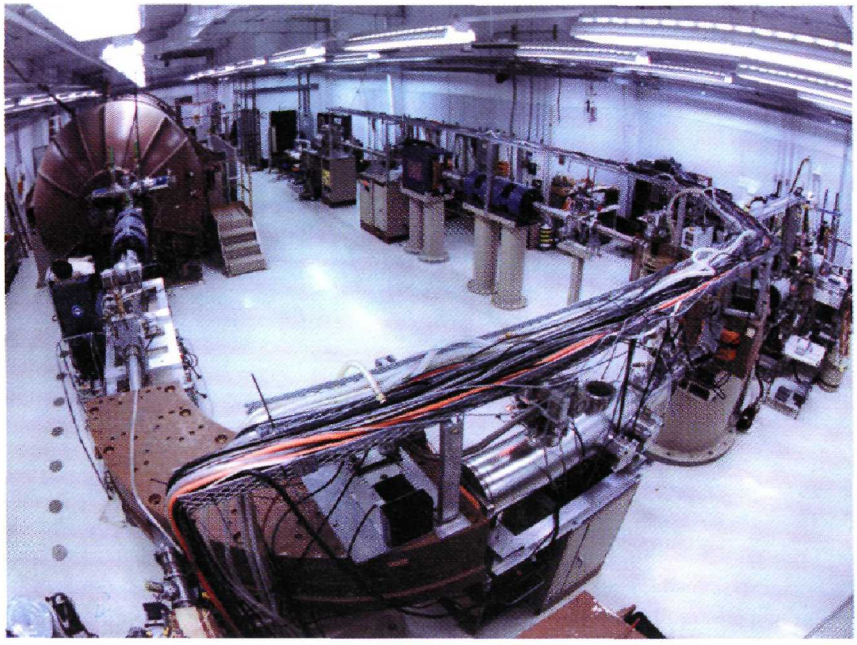


Figure 1. AMS system at Lawrence Livermore National Laboratory.



Lawrence Livermore National Laboratory's high-energy spectrometer and particle counter.

sity in the 3+ state. BeO^- is a more intense ion beam than Be^-, and overall efficiency is raised using the molecular ion. Acceleration of mass 26 ($^{10}Be^{16}O^-$) produces $^{10}Be^{1+...4+}$, $^{16}O^{1+...8+}$, and $^{10}B^{1+...5+}$, but the high-energy ions may also include $^{1}H^{1+}$, $^{7}Li^{1+...3+}$, $^{9}Be^{1+...4+}$, $^{11}B^{1+...5+}$, $^{12,13}C^{1+...6+}$, $^{14,15}N^{1+...7+}$, $^{17}O^{1+...8+}$, $^{19}F^{1+...9+}$, and so on, from other mass 26 negative molecular ions. Many of these molecular isobars are suppressed in the ion source by careful chemical preparation of the sample. Very small amounts of positive molecules may emerge with low charge states (1+ or 2+), but none survive in the 3+ charge state.

A magnetic quadrupole lens focuses the desired isotope and charge state to the entrance of the second dipole mass spectrometer and removes many ions by defocusing them into side walls. Most interfering ions after this magnet arise from collisions between residual gas (pressure $\sim 10^{-7}$–10^{-8} torr) in the beam pipes and the comparatively large numbers of positive ions. Their rigidity (momentum per charge) differs from the rare ion's, and a second dipole magnet removes them. Interfering ions with correct rigidity but incorrect momentum per mass (velocity) are then deflected vertically by crossed electric and magnetic fields in a Wien filter.

Light- to medium-mass isotopes (3–50 amu) are easily identified as they slow to stop in a multianode gas ionization detector that compares specific energy loss (amount of energy lost in collisions with gas electrons in part of the path) with the total energy loss of each particle. Figure 2 shows an example of the two-dimensional separation of ions by specific energy loss versus total energy loss in the detector, with identifiable peaks of well-separated isotopes. Other detection schemes are used to separate difficult isobar pairs, such as ^{36}Cl from ^{36}S in a gas-filled magnet, heavy isotopes such as ^{129}I and ^{127}I with time of flight at low energies, or ^{59}Ni from ^{59}Co by characteristic X-rays in a stopping foil (*1, 2*).

Absolute isotopic concentrations are not determined with AMS because the overall detection efficiency is small (a few percent), and both the production of negative ions in the source and the charge-changing process are velocity, hence mass, dependent. A stable isotope of the same element from the sample is selected sequentially with the rare isotope and is integrated in a Faraday cup at an off-axis position after acceleration and mass analysis. The ratio of rare-ion counts to this integrated ion current corrects for first-order variations in the production and transmission of the ions from the source through the high-energy analysis. (The transmission of the rare ions from the first dipole to the final detector is known to be constant and near 100%.) The isotope ratios from standards and blanks are measured in sequence with unknown samples to provide normalized isotope concentrations for the samples. AMS has been developed most completely for counting ^{14}C, but it can also be used to measure concentrations of ^{3}H, $^{7,10}Be$, ^{26}Al, ^{32}Si, ^{36}Cl, ^{41}Ca, ^{53}Mn, $^{55,60}Fe$, $^{59,63}Ni$, $^{81,85}Kr$, and ^{129}I, whose half-lives range between 12 years and 16 million years.

Precision, sensitivity, and throughput

With constant spectrometer conditions, the counts of individual rare ions are as random as the sputtering process in the ion source. As with decay counting, this process should follow Poisson statistics, and the uncertainty of the final isotope ratio is dominated by the counting statistics of the rare isotope in the unknown and the standards. Overall precision is best determined from the standard deviation of a number of measurements on equivalent samples. The most rigorous tests of precision are made for radiocarbon, where demands are greatest. We usually observe variations with respect to the international radiocarbon standard equal to, or only slightly greater than, our expected Poisson statistics of about 0.5–1 %. Precisions for other isotopes range from 1 to 5%.

Accuracy of final isotopic ratios from AMS is determined by comparisons with known standards and with high-accuracy counting measurements. Intercomparisons among AMS laboratories will establish international standards for isotopes that are impossible to decay count. An international standard already exists for ^{14}C, and a recent check on accuracy in ^{14}C dating showed that AMS accuracy is within the precision established by the eight laboratories involved (*12*).

The sensitivity of AMS is limited by indistinguishable interferences in the detector/counter, but some of those can be removed by careful chemical preparation. For example, ^{14}N does not form a negative ion, leaving ^{14}C with no atomic isobar interference. Calcium is analyzed as trifluoride or trihydride ions that are stable, whereas potassium molecular isobars are not. Borosilicate glass is avoided in preparing beryllium samples because leached

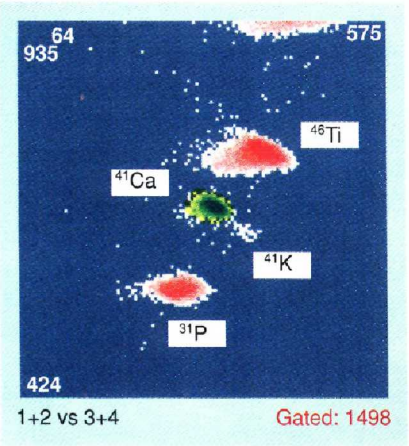


Figure 2. Identification and counting of individual ions.

Energy deposited by the ion slowing in the first half of the detector is plotted against the energy lost in stopping in the second half. Colors indicate the number of ions having that energy distribution. The ^{41}Ca peak is "painted" in different colors to mark the events (1498) identified as ^{41}Ca. Despite the several-sector filtering, other ions entering the detector include ^{31}P and ^{46}Ti.

^{10}B contributes a large mass –10 interference, and ubiquitous ^{36}S limits the sensitivity for ^{36}Cl in some detectors.

Finally, artificial contamination or even the natural level of an isotope in a preparation laboratory can limit sensitivity. For example, the contemporary biosphere contains radiocarbon at concentrations 3 orders of magnitude greater than those in 50,000-year-old samples. To date late Pleistocene samples, recent organic contaminants must be removed to parts-per-thousand levels. With careful chemical preparation, AMS has a dynamic range of isotope ratios from 10^{-15} to 10^{-8} in milligram-sized samples, which corresponds to detection sensitivities of attomoles to picomoles. The upper limit of detection is determined by the count rates in the final detector and memory effects in the ion source. Table 1 shows typical sample sizes and sensitivities routinely achieved for some isotopes commonly measured by AMS.

The throughput of AMS is a function of sample preparation chemistries, ion source efficiency and intensity, system transmission, detector live time, and desired precision. Many constraints are linked to the ion source output. Operating with source currents of ~ 100 μA C^-, we make 50–80 radiocarbon dates in a day's operation to precisions of 0.5–1%. Other labs reach 0.2–0.5% precision by measuring 20 or fewer samples per day at 10–50 μA source currents. Biomedical ^{14}C tracing has a throughput of 200–300 measurements per day, because lower precision (1–5%) is acceptable. ^{10}Be, ^{36}Cl, ^{41}Ca, and ^{129}I measurements are slower and less precise; 20–50 samples are measured with 2–5% precision in a day.

An AMS measurement usually requires a few minutes of instrument time, but determining the sample definition and chemistry often takes longer. Thus, in many cases, the AMS instrument is not the factor limiting throughput. Throughput can be increased by preparing many samples in parallel, using robots to automate sample preparation, or using an AMS instrument to serve a number of clients who perform their own definitions and sample preparations. In this case, each client is responsible for the standards and background samples required to interpret the results.

Sample definition

Current AMS ion sources require samples that are thermally and electrically conductive solids. This material is further constrained by effective chemical isolation of the sample from its matrix. The isolation process must be nonfractionating or minimally fractionating, efficient, and protected from contamination by isobars or unexpected concentrations of the rare isotope in or on laboratory equipment. Uniformity and comparability between samples and standards are ensured by reducing all samples to a homogeneous state from which the final target material is prepared. Carbon samples (^{14}C) are combusted or hydrolyzed to CO_2 before reduction to graphite, commonly produced by the reduction of CO_2 by hydrogen or zinc over an iron catalyst and binder.

Hydrogen (^{3}H) in an oxidized sample is reduced from the resultant water by titanium and disperses within the metal as a hydride. Halides (^{36}Cl and ^{129}I) are precipitated by silver from the acid-solubilized sample. Aluminum (^{26}Al), beryllium (^{10}Be), and calcium (^{41}Ca) are homogenized as solutes before precipitation and conversion to an oxide, fluoride, or hydride. In all cases, the bulk isotopic signature of the sample is retained, but all other chemical and physical information is lost. All of the "science" in the AMS measurement is in the physical and chemical definition before homogenization. Many analytical separation techniques are used in sample definition, from simple physical separation of components visually identified under a microscope to chemical separation by differences in solubilities to chromatographic and electrophoretic processes.

Contamination with the isotope being measured must be prevented or quantified before homogenization. Spurious isotopes are incorporated in a sample from a surrounding matrix, through natural irradiation (in situ production), during sample definition, and during chemical preparation. The latter two are most prevalent in isotope tracing, in which large concentrations of the isotope exist in the same laboratory as the samples. The small-sample capabilities of AMS allow measurement of contaminant levels in extracted components for assessing the nature and extent of matrix contaminations still left in the sample.

Analytical processes often produce samples that are too small for current methods of presentation in an ion source. In these cases, an isotope dilution is done by adding to the sample carrier compounds with well-known isotope concentrations before or during the homogenizing phase of preparation.

For example, the concentration of native ^{9}Be in oceanic samples is typically very low and spatially variable, primarily because of continental erosion. Natural ^{10}Be, however, arises from stratospheric production and subsequent fallout modulated by geomagnetic and transport variations. A few milligrams of ^{9}Be carrier as a beryllium salt are added to samples before extracting the beryllium from aquatic or sedimentary samples. The added ^{9}Be greatly overwhelms variable native ^{9}Be, decoupling the measured ^{10}Be concentration from the native ^{9}Be.

Similarly, microgram biochemical isolates from HPLC or electrophoresis can be diluted into milligram amounts of low-^{14}C carriers before combustion and reduction. The concentrations of isotopes in the isolates can then be derived from the measured isotope ratios and the carrier masses.

Applications

The sensitivity of AMS makes possible new approaches to detailing the geomorphological changes wrought by the ice ages of the past 2 million years. AMS has also expanded oceanic tracing capabilities and has provided new tools for paleoclimate reconstruction. It enabled a microchemistry revolution in radiocarbon dating methods that provide the underlying chronological basis for studies in archaeology, paleoclimatology, and paleoecology, and it was recently adapted to tracers in biomedical and chemical studies. Some applications of AMS in quantifying heavy trace elements for geological research (*13*) and in finding impurities in semiconductor materials (*14*) overlap other techniques such as resonance ionization MS or ICPMS. These techniques quantify a broader range of elements and isotopes, but neither is as sensitive as AMS for selected elements and matrices.

Table 1. Isotopes commonly measured by AMS

Element	Isotope	Half life (years)	Sensitivity (parts per 10^{15})	Chemical form in ion source
Hydrogen	^{3}H	12.3	0.1	TiH_2
Beryllium	^{10}Be	1.6×10^{6}	5	BeO
Carbon	^{14}C	5730	2	Graphite
Aluminum	^{26}Al	720,000	3	Al_2O_3
Chlorine	^{36}Cl	300,000	5	AgCl
Calcium	^{41}Ca	105,000	2	CaF_2,CaH_2
Iodine	^{129}I	16×10^{6}	10	AgI

Earth science. Radionuclides are used in the earth sciences both as chronometers and as tracers. AMS has had a revolutionary impact on these fields, allowing routine measurements on very small samples and new isotopes, and replacing overview data sets with large, detailed ones (*15–18*).

The mixing of the ocean is an important influence on global climate, and the relative age differences among surface and deep water masses are especially important in understanding the rates of this mixing. Paleocirculation patterns can be determined by the difference in ^{14}C content between surface-living forams and deep-living species because ocean sediments retain both types in relative chronological layering. AMS measurements need only a few hundred micrograms of carbon, so "only" hundreds of single-species forams, each weighing only ~ 5 μg, must be hand-picked from layers of sediments to trace circulation patterns over time.

The thermal history of the North Atlantic after the last glaciation, particularly important in testing climate models, is also recorded in ocean sediments. Evidence of specific climatic variation is detected: "Heinrich Events," effects seemingly caused by periodic advances of sea ice and associated ice-borne clasts during the general transition from the Pleistocene Ice Age to the Holocene moderate climate, have worldwide effects, as shown by ^{14}C dating that relates North Atlantic forams and South American lake sediments (*19*).

Pollens in lake sediments indicate past climate by recording the plant species in the region of the lake at different times. Dates of these pollen assemblages, based on undifferentiated bulk carbon in the sediment, are influenced by remobilized carbon of earlier deposits, such as redissolved carbonate from limestone, which leads to a "reservoir" effect that causes sediments to appear older than they actually are. AMS circumvents this problem by measuring actual biologic remains—either pollen or macrofossils such as bits of leaf or other recognizable organic residues that are more likely to be contemporaneous with the sediment deposit (*20*).

Surface exposure dating, which measures the cosmogenic radionuclides produced when energetic particles (cosmic rays) hit the Earth, was impossible before AMS because traditional counting methods could not measure the small amounts of radionuclides present. A sample on the Earth's surface for 10,000 years (the time since the end of the last continental glaciation) will accumulate 500,000 atoms of ^{10}Be in 10 g of quartz, an amount of ^{10}Be that is just measurable by AMS; longer exposure will increase the concentration of ^{10}Be. The use of AMS, which can detect longer lived cosmogenic radionuclides such as ^{10}Be, ^{26}Al, and ^{36}Cl, has allowed dating of the Pleistocene period, when major glaciations reformed the surface of the Earth and during which *Homo sapiens* developed.

For example, the use of all three radionuclides has made it possible to determine the age of the Meteor Crater in Arizona. The impact exposed large blocks of Kaibab dolomite that were shielded from cosmic rays before the impact, and sampling of the tops of ejecta blocks yielded a ^{36}Cl age of 49,700 ± 850 years (*21*) and a $^{10}Be/^{26}Al$ age of 49,200 ± 1700 years (*22*). These ages agree well with an earlier thermoluminescence age of 49,000 ± 3,000 (*23*).

Cosmogenic radionuclides can also be used as tracers. Because they, along with other atmospheric components, were trapped by the falling snow forming the ice sheet, polar ice cores archive atmospheric constituents covering at least the past 120 kyr. The concentration of nuclides at different depths in the ice, corresponding to different times, reflects the incident cosmic ray flux, the solar activity, the strength of the Earth's magnetic field, the mode of atmospheric mixing, and the precipitation pattern over the ice sheet at the time of the snowfall. The 11-year solar cycle is recorded in these radionuclide concentrations and can be studied for times well before the record of visual sightings of sunspots. Other variations include the change in concentration at the end of the last glacial period (probably caused by changes in snow accumulation rate) and the large concentrations at about 40 kyr, which indicate a global event of as-yet undetermined cause, perhaps a geomagnetic excursion or a supernova event.

Radiocarbon dating. The original impetus for AMS came from attempts to improve and expand radiocarbon dating. AMS radiocarbon dating was developed in the midst (and with the enthusiastic aid) of a mature, flourishing radiocarbon dating tradition based on β-decay counting. In all fields that use radiocarbon chronometry, there are difficulties in finding re-

liable samples of adequate size for β-counting. AMS not only required smaller whole samples but also allowed a microanalytical revolution in defining the dated materials. A few examples from archaeological applications will illustrate what is now possible, but the full potential of the method has not been exploited.

It can be difficult to find archaeological samples for radiocarbon dating that are directly connected to the human event of interest. A measurement on a piece of charcoal dates tissue formation in a tree, not an ancient barbecue. Furthermore, samples that are directly traceable to humans are often too small for rigorous sample purification methods, and the material itself may be very precious, a fact that makes it impossible to remove large pieces for dating. AMS measurements, however, can be used on precious objects with no apparent damage. Perhaps the most famous (or infamous) are the measurements done on threads from the Shroud of Turin, the cloth in which Jesus Christ was purportedly wrapped for burial. AMS radiocarbon dates showed the cloth to be from the 14th century AD (*24*).

AMS has been used to reexamine a number of controversial sites and artifacts. After an AMS measurement of a barley seed found in the 18,000-year BP level of an Egyptian site yielded an age of only about 8000 years, a postulated very early age for the development of agriculture was abandoned. In another example, a conventional radiocarbon age on a bone artifact (the "Old Crow flesher") from the northern Yukon provided important but disputed evidence for the presence of humans in the New World 27,000 years ago. Until the advent of AMS, insufficient material remained for retesting, but AMS analysis of a small portion of collagen from the remaining artifact dated it in the early 8th century AD.

Similarly, redating purified collagen from other human bones purported to be older than the Clovis culture (~ 11,000 years ago) in North America has shown that the earlier dates on less well-defined chemical fractions are incorrect. Inorganic fractions of buried bones contain exchanged carbon from dissolved species in groundwater, but contamination of purified proteins is less likely. Because hydroxyproline is a significant component of bone collagen but is rare in other natural proteins, further specification of the dated carbon is done by hydrolyzing collagen to component amino acids, which are dated by AMS (*25*).

AMS has also been used to determine the time of actual use of a flaked stone tool by dating residues of blood and tissue on the tool (*26*) and to date the charcoal pigments in cave art (*27*). It is clear that, with further application of analytical and separative chemistry, it will be possible to identify and isolate materials that provide reliable ages directly associated with human activity.

Biological and environmental tracing. In biomedical science, where a tracer isotope and its concentration are chosen by the researcher, the AMS advantage is less recognized. Elements that previously had no suitable tracer isotopes are now studied with AMS using very long-lived isotopes (^{26}Al, ^{36}Cl), and low-dose tracing over very long periods of time is now possible for other nutritive and/or toxic elements (^{10}Be, ^{41}Ca, ^{79}Se, and ^{129}I). In several cases, these isotopes supplant a shorter lived isotope, decreasing both radiation and chemical doses in studies of elemental metabolism.

The full potential of AMS in radiocarbon dating has not yet been realized.

AMS also is advantageous in detecting attomoles of ^{14}C-labeled biomolecules from natural systems because it directly traces the concentration of a prelabeled compound over 5 orders of magnitude, with wider ranges available through isotope dilution. The unique capabilities of AMS for the life sciences include high throughput, large dynamic range, sample-independent analysis methods, and high sensitivity.

^{26}Al and ^{41}Ca are especially useful for tracing elemental metabolism. Humans evolved with aluminum oxide in their environment, but not with elemental aluminum, which was introduced by refining techniques in the last century. AMS tracing has thus far indicated the presence of several pools of interacting aluminum storage in the body that will require detailed physiological tracing (*1*).

The rare stable isotopes of calcium can be detected with IRMS and are used in tracing calcium metabolism. However, compared with enriched stable isotopes, ^{41}Ca is less expensive to produce, has greater sensitivity over background, and allows lifelong studies. A 100-ng dose of ^{41}Ca administered to a human reached an equilibrium isotope ratio of 10^{-11} (^{41}Ca to ^{40}Ca) and will remain constant in this subject for years to come (*28*). Variations on this ratio reflect dietary changes and bone resorption caused by hormonal changes or osteoporosis.

Tracing ^{14}C-labeled compounds through natural systems is the most widely used application of biomedical AMS. Researchers in the life sciences are familiar with ^{14}C and ^{3}H, for which numerous labeled compounds are commercially available. However, the differences between ^{14}C concentrations for decay counting and AMS are so great that many biomedical and environmental research laboratories have contamination levels preventing their use of AMS.

We use ^{14}C-labeled compounds at levels of exposure directly relevant for humans to determine the bioavailability, biological half-life, and dosimetric parameters of toxicants, particularly carcinogens, at very low exposure levels (e.g., 1 ng/kg). AMS can also be used to study rare molecular binding events, such as adduction of carcinogens to specific organ DNA at low dose in vivo. Such binding is measured by AMS to levels of 6 adducts per 10^{12} nucleotides, equivalent to the formation of 6 adducts per 1000 cells. No threshold effects have been detected in the dose responses for chemicals studied to date.

Because AMS greatly reduces the chemical and the radiological dose (typically 10 nCi or less) administered to the subject, human studies can be conducted for validation of animal models and for clinical applications. For example, if the DNA damage caused by the heterocyclic amine carcinogen 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline

(MeIQx) is similar in man and in the Spraque–Dawley rat (*29*), the level of tagged chemical necessary to detect DNA damage corresponds to a 0.003 mSv effective dose equivalent per administration (about 5% of the effective radiation dose from a chest radiograph). In the clinical arena, the use of AMS could dramatically reduce the amounts of labeled substrates administered during noninvasive tests for diagnosing diseases or for phenotyping metabolic characteristics. Although such clinical applications have yet to be demonstrated, they may ultimately be a major contribution of AMS in the life sciences.

Finally, AMS can be coupled to HPLC, TLC, and electrophoresis for determining specific modified nucleotides, metabolites, and proteins in the search for molecular targets of labeled compounds. HPLC-based studies of DNA adduction and metabolite production with ^{14}C-labeled compounds have shown column sensitivities of 100 ±10 zmol.

Our experience shows that both natural and biomedical samples are compatible in a single AMS system, but few other AMS sites make routine ^{14}C measurements for both dating and tracing. AMS is, in one sense, just "a very sensitive decay counter," but if AMS sensitivity is creatively coupled to analytical chemistry of certain isotopes, whole new areas of geosciences, archaeology, and life sciences can be explored.

This work was performed under the auspices of the U.S. Department of Energy at the Lawrence Livermore National Laboratory by the University of California under contract W-7405-Eng-48. Portions of this work have been supported by the National Institutes of Health (CA55861-01; ES04705-07), the U.S. Army Breast Cancer Program (MM4559FLB), and NSERC/Canada.

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