burden. Evidently, nobody is interested in using him. On the contrary, there is a tendency to lower him in the social ladder and to make difficult in every way his admission to his profession and to the society of his colleagues. The conclusion is reached that, speaking of the value of scientists, the Authorities have in mind not us, but those of our colleagues whom they suppose to frighten with the sight of our outcasting and, so to say, fall. The scientists must see in our example what awaits them in case of disobedience—the loss of work, the end of the scientific career, personal insecurity and a quite doubtful possibility of emigration.

Even though the desire to live in the Jewish State might be connected with national, family or religous motives, our forcible detention in the U.S.S.R. draws us into this political game, the winning stake in which is the uncontrolled use of the creative potential of obedient scientists.

On 12 May, the *New York Times* printed a letter from the Israeli scientists, Gileadi, Jortner, and Kosower, saying, "It is urgent that everything possible should be done to aid Professor Levich to make a free choice concerning his scientific career. Past experience has shown that the authorities of the Soviet Union are quite sensitive to public pressure on matters of scientific freedom."

The most direct appeal to an American institution on Levich's behalf occurred when Alan Bard, professor of chemistry at the University of Texas, presented a possible motion to a 11 May meeting of the board of directors of the 4000-member Electrochemical Society. The statement urged that the board "strongly endorse the principle of scientific freedom and the right of scientists to choose the location where they practice their professions. . . . We strongly urge that Professor V. G. Levich and other scientists of the U.S.S.R. requesting emigration permits be granted these and be allowed to leave when they desire. . . ."

However, after what Bard and the president of the society, C. W. King of American Gas and Chemicals, Inc., describe as a "friendly" discussion, all agreed that the motion would not be taken up or formally considered, both because the facts of the Levich case seemed uncertain at the time and because it might not be the proper subject for consideration by the technical group. In addition, a board member said later, the Electrochemical Society's membership in Eastern European countries ruled out any official action on the case of the Russian.

Aside from the Tel Aviv group, a number of U.S. scientists have written letters to National Academy of Sciences officers concerning the Levich situation. According to spokesmen at the Office of the Foreign Secretary of the academy, the subject was mentioned at a June meeting of the academy council at which it was decided that private action would be preferable to any public, official moves.

Debate over How to Help

The Levich situation illustrates the delicacy of American scientific relations with the Soviet Union. While many scientists want to aid Levich, there is considerable disagreement as to what will help or hurt.

One view is that the harassment of Russian scientists by their own government—by such alleged means as visa denials, mail censorship, demotion, firing, and so forth—cannot properly be the business of another country. Another view is that all cases are individual, that no blanket policy can be made.

However, some American scientists believe that giving wide publicity to cases of harassment, and public protests outside of the U.S.S.R. will prove effective. They cite the widespread alarm generated by the news that biochemist Zhores A. Medvedev had been confined to a psychiatric ward with a diagnosis of schizophrenia based on some of his statements. They argue that the publicity surrounding Medvedev's treatment caused embarrassment to Soviet authorities and ultimately helped bring about his release.

Other U.S. scientists are equally adamant, but insist the opposite—that only discreet, private contacts will help colleagues in Russia. The less publicity these contacts receive, the better.

Standing between these two views is physicist Bernard Feld, a long-time participant in the Pugwash conferences, who is not adverse to publicity for these situations. However, he says, "One is caught not knowing what pressures are most useful. . . . Loud public protest may have a tendency to harden the bureaucrat. . . . What seems most useful is individual letters to people in the field in the Soviet Union." A few weeks ago, the United States and the U.S.S.R. agreed to a joint commission for science and technology. While it would appear unlikely that the commission will be able to take up the case of any individual, the very existence of such a cooperative body could signal freer movement of Russian scientists in the future.—DEBORAH SHAPLEY

RESEARCH NEWS

Stable Isotopes: Expanded Supplies May Lead to New Uses

The stable but uncommon isotopes of carbon, nitrogen, oxygen, and other biologically significant elements have interested chemists for a long time. Unprecedented amounts of these isotopes, hitherto available only in gram quantities, are now being produced at the Los Alamos Scientific Laboratory (LASL) in New Mexico as part of an Atomic Energy Commission (AEC) effort to increase their use and lower their cost. This effort, the prospect of still larger quantities, and improvements in the instruments used to detect stable isotopes have stimulated renewed interest and applications in structural chemistry, biochemistry, and clinical medicine.

Like the now widely used radioactive isotopes such as ^{14}C, the greatest potential value of the stable isotopes appears to be associated with their use as tracers that enable scientists to follow chemical transformations and to study the interactions of labeled compounds within complex biological systems. Among other proposed uses, these nonradioactive tracers might make possible

diagnostic studies in pregnant women and routine screening of large populations, uses for which radioactive substances are not desirable. Applications to agricultural and ecological problems, and even to the problem of tracing the sources of illegal drugs or of oil spills, are also being put forward. Research with stable isotopes is, for the most part, still in a very preliminary state, but enthusiasm and impatience for supplies of labeled compounds are running high in many laboratories.

Carbon-13 constitutes 1.1 percent of the earth's carbon atoms, and the natural abundances of ^{15}N and the heavy oxygen isotopes are even less (see Table 1). Each of these isotopes differs in its physical and chemical properties only very slightly from the more abundant species, and it is consequently difficult to separate them. As recently as 3 years ago, the price of ^{13}C was about $4000 per gram and only limited amounts were available from such suppliers as Prochem in Great Britain or the AEC (there are no commercial suppliers of these isotopes in the United States, although several companies synthesize labeled compounds from isotopes obtained elsewhere). This cost has now been greatly reduced to about $60 per gram as a result of AEC efforts to increase the supply and stimulate the use of these isotopes. About 1 kg of ^{13}C is produced every year at the AEC's Mound Laboratory in Miamisburg, Ohio, and larger quantities are being separated at LASL. Much of this is being used by the AEC, but about 2 kg of ^{13}C per year is available to the general scientific community from the Mound facility, which acts as distribution center.

Conventional distillation methods at low temperature are used by B. B. McInteer and Robert Potter at LASL to separate the isotopes. Carbon monoxide is fed into one of several columns (each 140 feet long) that are cooled with liquid nitrogen. Small isotopic differences in vapor pressure (less than 1 percent) lead to preferential evaporation and concentration of ^{13}C carbon monoxide at the bottom of the column and ^{12}C carbon monoxide at the top. Similar procedures are used to separate nitric oxide into isotopic fractions.

The column is surrounded by a vacuum chamber to minimize heat leaks. Nonetheless, the plant consumes about 1000 liters of liquid nitrogen per day, which accounts for the main expense of operating the facility. The highly automated plant operates 24 hours a day under normal conditions, and it is currently producing about 5.0 kg of 90 percent enriched ^{13}C per year and smaller quantities of 99 percent enriched ^{15}N and 30 percent enriched ^{17}O. As a side product, large quantities of extremely pure ^{12}C, ^{14}N, and ^{16}O (depleted in the other isotopes) are also produced. A much larger plant that will have ten times the present capacity is now under construction at Los Alamos.

Table 1. The stable isotopes of carbon, nitrogen, and oxygen.

Isotope	Relative abundance (%)	Nuclear spin
^{12}C	98.9	0
^{13}C	1.1	$^1/_2$
^{14}N	99.6	1
^{15}N	0.4	$^1/_2$
^{16}O	99.8	0
^{17}O	0.04	$^5/_2$
^{18}O	0.2	0

With few exceptions, the isotopes obtained from this separation process are not useful for tracer studies until they have been synthesized into biochemically interesting compounds. A major effort to produce such compounds in large quantities for use in AEC programs is under way at LASL, under the direction of Donald Ott of the laboratory's health division. Both biosynthesis, with the use of algae, yeast, and other organisms, and the more time-consuming lab-bench methods of organic synthesis are being used, with priority being given to the preparation of labeled compounds for clinical trials. Among the compounds that have been prepared chemically are cyanide, cysteine, glucose, and urea labeled in various ways with ^{13}C or ^{15}N, and work is proceeding on the synthesis of several labeled amino acids such as tryptophan.

Biosynthesis of Labeled Compounds

Organic syntheses are used to prepare specifically labeled compounds in which particular atoms are replaced by another isotope, but the LASL group has found that for complex materials and for uniformly labeled substances (in which every atom of an element has the same mass number) biosynthesis is the preferred method. They are producing large quantities of uniformly labeled galactose by incubating a marine kelp in an atmosphere of ^{13}C carbon dioxide, and then chemically separating out the sugar. Several species of algae are being used, and a yeast, *Candida utilis*, was successfully grown on acetate.

A variety of analytical methods for detecting the presence of labeled compounds are being employed at LASL and in other laboratories. The methods depend either on the difference in mass between the isotopes or on the nuclear spin and resulting magnetic moment of ^{13}C, ^{15}N, and ^{17}O (see Table 1). Mass spectrometers, in which the ionized particles that are to be analyzed are accelerated in an electric or magnetic field, appear to be the most popular instrument for routine analysis. Infrared spectrometers, which measure the change in the vibrational frequencies of a molecule with increased mass, are also being considered. For complex macromolecules, the separation of labeled material with ultracentrifuges and similar isopycnic techniques is being considered.

A more expensive but potentially more sensitive instrument, especially for studies of molecular structure, is the nuclear magnetic resonance (NMR) spectrometer. The NMR technique not only measures concentrations but also provides information about the characteristics of the chemical environment around a particular atom. Because the natural abundance of ^{13}C, for example, is low, there are few background signals and the signals are relatively simple. The method has the advantage that intact molecules can be nondestructively analyzed. Other methods that depend on nuclear spin, such as electron spin resonance and proton resonance, are also being used.

Recent improvements in NMR techniques in which multiple spectra are obtained and the signals are analyzed and averaged by a computer have increased the sensitivity of the method by several orders of magnitude, with the result that investigators in several laboratories are now able to conduct ^{13}C studies of unenriched (naturally occurring) substances. Indeed, ^{13}C NMR spectroscopy is already a diverse and active field of research. David M. Grant of the University of Utah, for example, has used the technique in studies of the temperature dependence of ^{13}C spectra to obtain thermodynamic information about kinetic processes, such as the conformational interconversions of cyclohexanes (*1*). John Roberts of the California Institute of Technology has studied the molecular dynamics of many small molecules with ^{13}C NMR. J. B. Stothers of Western Ontario University in London, Ontario, has found the method useful for studying reaction mechanisms, and Jacob Schaefer of the Monsanto Company in St. Louis, Mis-

souri, has studied the structural details and stereochemistry of polymers (*2*). Grant is now using ^{13}C NMR to study large molecules such as insulin, whose crystalline structure is known from x-ray work, but whose behavior in solution is largely unknown; by measuring relaxation times for the change from one nuclear spin state to another, he hopes to obtain detailed information about the relative motions of segments of the molecule and hence to understand some of its structural dynamics.

More specific and more sensitive structural studies of organic molecules will be possible with enriched ^{13}C materials. Some work on the structure of tetrapyrroles (chlorophyll-like compounds) has been done by Nick Matwiyoff and his collaborators at LASL, and Charles Gregg and his associates, also at LASL, are beginning studies on labeled ferredoxins (biologically important organometallic proteins that act as enzyme catalysts) and on the conformational changes of hemoglobin. Studies of biosynthesis with labeled compounds have also begun; LeRoy Johnson, formerly of Varian Associates in Palo Alto, California, and Masato Tanabe of the Stanford Research Institute have grown mold cultures on labeled acetate, and with NMR spectroscopy have been able to determine some of the biosynthetic pathway by which the antibiotic asperlin, separated from the culture, is formed (*3*).

In addition to fundamental research applications, there is considerable interest in clinical applications of stable isotopes for the diagnosis of metabolic diseases and similar problems. At LASL this interest is motivated in part by the awareness that clinical uses would create a large demand for these materials and hence help to reduce their price.

Under the direction of Walton Shreeve of Brookhaven National Laboratory, a visiting staff member at LASL, a collaborative program has been established with the University of New Mexico Medical School in Albuquerque to begin clinical trials of a test for diabetes. Glucose that has been labeled with ^{13}C will be given to patients in a glucose tolerance test. According to the proposed method, samples of the patient's breath would be collected and its carbon dioxide content would be analyzed to determine the $^{12}C/^{13}C$ ratio. Shreeve believes that this technique would be a simpler clinical procedure than the present method of collecting multiple blood samples for blood sugar analysis. Although the effort is still exploratory, its proponents expect to find a lower concentration of ^{13}C in the breath of diabetics as evidence that they have trouble metabolizing the sugar.

Diagnostic procedures for other metabolic problems are being planned as well. Shreeve believes that thyroid and some liver diseases may be identifiable with stable isotope tracers, and he cites as support for this view the earlier investigations of many of these malfunctions with ^{14}C and other radioisotopes. Studies with stable isotopes of genetic abnormalities, such as galactosemia, and of malabsorption of fats and carbohydrates, are also planned. Although the stable isotope method is not as sensitive as those involving the more readily detectable radioisotopes, Shreeve believes that mass spectrometry can provide sufficiently accurate measurements to be of clinical use. Still greater sensitivity and versatility could be achieved with doubly labeled compounds.

Studies with ^{13}C Mice

Glucose labeled with ^{13}C has been approved by the Food and Drug Administration for investigative use, and other labeled compounds are awaiting such approval. But a still unanswered question concerning the possible clinical use of stable isotopes is their toxicity. Little is known about the effects of specific isotopes on the chemistry of man or other higher organisms, although most investigators believe that the effects of ^{13}C, for example, will turn out to be insignificant, because the mass differences between ^{12}C and ^{13}C are small. No formal toxicity studies have been done, but an experiment was carried out at LASL to demonstrate that no overt biological effects occur even with extremely high concentrations of ^{13}C. Two mice, one of which apparently asphyxiated before the completion of the experiment, were fed exclusively on ^{13}C yeast, and they ultimately reached a 70 percent ^{13}C concentration in their total body carbon, far higher than would result from any normal applications of stable isotopes. The ^{13}C mice showed normal weight gain and no evidence of pathology or morphological abnormalities, according to the LASL investigators.

Clinical uses may not be the only large-scale potential market for stable isotopes. Although originally thought of as by-products of the separation process, the ^{14}N and ^{16}O (isotopically pure to within several parts per million) have turned out to be useful materials in their own right. In the inverse of the usual tracer experiment, ammonium sulfate which is depleted in ^{15}N will be used to study the movements of nitrogen added to agricultural land as fertilizer. A large, 6-year field study is being conducted by Perry Stout of the University of California at Davis and his colleagues in which a metric ton of ^{14}N will be added to a 0.1-acre plot under realistic farming conditions—an amount equal to about one-half of the native nitrogen in the organic matter of the soil. By sampling for the depletion of ^{15}N, the investigators hope to determine quantitatively the fraction of the fertilizer nitrogen that ultimately reaches the groundwater, becomes part of the soil organic matter, undergoes denitrification, or is taken off in crops. Stout estimates that a 30-fold dilution of the original nitrogen will be detectable, possibly enough to permit investigators to trace its progress from the crop (corn) through chickens, cows, and other parts of the human food chain.

Still another use has been found for the purified ^{16}O. Plutonium oxide (PuO_2) is being manufactured as a power source for use in space vehicles and heart pacemakers. Replacement of normal oxygen with ^{16}O and the virtual elimination of ^{17}O from this preparation reduces the neutron radiation produced by the reaction of α-particles from the radioactive decay of plutonium with the loosely bound neutron in ^{17}O.

The AEC faces a number of unique problems in its efforts to promote the expanded use of stable isotopes. Although it is making these isotopes available for cooperative research programs to several other federal agencies, the AEC finds it more difficult to make these materials available to the general scientific community. By law, the agency cannot give them away, nor can it compete with U.S. commercial suppliers of the raw isotopes, should any appear. Hence the agency policy is to try to increase the supply while reducing the cost of the isotopes, but without lowering the price so far as to exclude commercial suppliers from entering the business when the market is sufficiently large. In view of the extent of scientific interest and the diversity of new applications for these long-neglected isotopes, that market is not likely to be very long in developing.—ALLEN L. HAMMOND

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