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PROCEEDINGS OF SEMINAR ON THE USE OF STABLE ISOTOPES IN CLINICAL PHARMACOLOGY, UNIV. OF CHICAGO, NOVEMBER 10–11, 1971

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Argonne, Illinois

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Los Alamos, New Mexico

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BIOLOGY AND MEDICINE

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PROCEEDINGS OF A SEMINAR ON THE USE OF STABLE ISOTOPES IN CLINICAL PHARMACOLOGY

November 10-11, 1971

The University of Chicago
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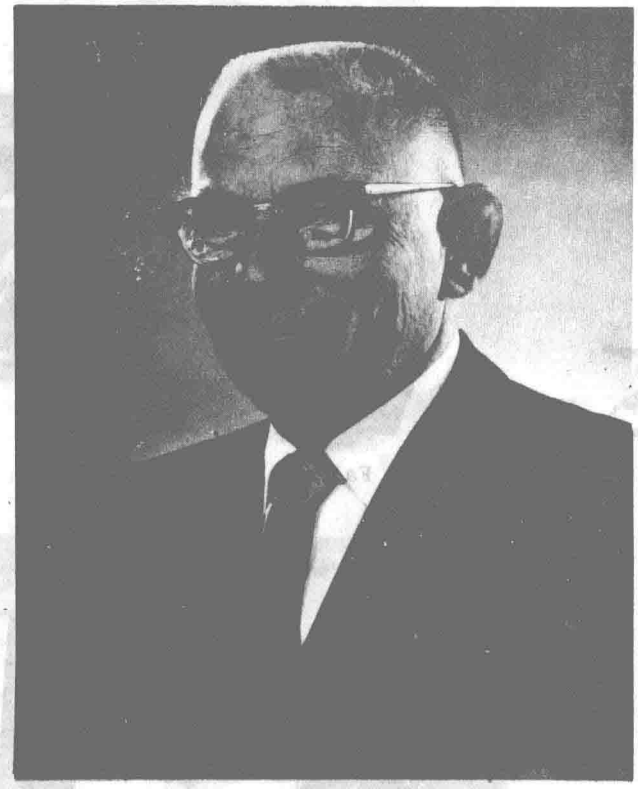

These Proceedings are dedicated

to

Eugene Sant Robinson

May 31, 1916 - June 22, 1972

Biemann

Berlin

Bush

DeGrazia

Fales

Freese

Gaffney

Goldstein

Hofmann

M. C. Horning

Kipnis

Klein

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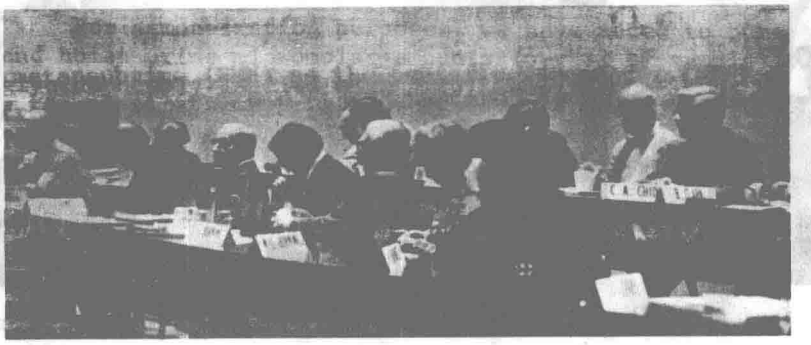

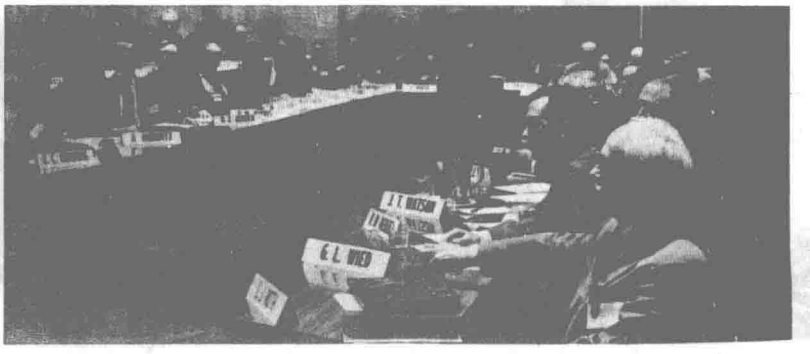

Photographs by E. S. Robinson

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INTRODUCTION

Lloyd J. Roth
Department of Pharmacology
University of Chicago, Chicago, Illinois

Welcome to the Seminar on the Use of Stable Isotopes in Clinical Pharmacology.

This meeting, organized by Peter Klein, Eugene Robinson, Bert Tolbert, and myself, grew out of a National Symposium on Carbon 13 held at Los Alamos on June 9-11, 1971 which was concerned largely with physical and analytical measurements. At that time it became apparent that a second meeting concerned with biological applications was desirable because the availability of stable isotopes would soon make possible many studies in the human which heretofore could be carried out only with radioactive tracers.

There is no doubt that the introduction of stable isotopes in clinical research will open a new era not unlike that which followed the distribution of radioactive isotopes on a commercial scale two decades ago.

The group here assembled is a heterogeneous one. Everyone is an expert in some area, but lacking expertise in another. Thus, in the best of all possible worlds, each will be able to participate in both the teaching and the learning process. It is in this spirit that we expect this gathering to provide the basis for a continuing dialogue between the participants long after this short contact.

Dr. Robinson's paper will open the meeting. It is a great pleasure for me to introduce him, because Robbie and I were graduate students in chemistry at Columbia University so long ago it is hard to remember. We went in divergent paths, and to come together at this meeting is a personal, if not a slightly emotional, experience for me.

CHEMICAL RESOURCES

Chairman: L. J. Roth

PRODUCTION OF STABLE ISOTOPES

E. S. Robinson

ORGANIC SYNTHESIS AND BIOSYNTHESIS

D. G. Ott

PRODUCTION OF STABLE ISOTOPES

Eugene S. Robinson
Chemistry and Nuclear Chemistry-4
Los Alamos Scientific Laboratory, Los Alamos, New Mexico

One thing that we at Los Alamos have discovered about isotopes is that if they are essentially free, or cheap, people will do experiments with them. If isotopes are kept at high prices, you may buy a gram at $1,000.00, but it sits on the shelf waiting for the definitive experiment, and no real use is made of it.

Stable isotopes are now being produced at the Los Alamos Scientific Laboratory due to the efforts of Dr. B. B. McInteer and his associates. The techniques they use involve cryogenic distillation of liquid carbon monoxide and liquid nitric oxide.

A typical system as developed by Dr. McInteer is shown in Figure 1. The carbon monoxide plant is in three sections, a single column of 80 feet for the enriching section at the bottom, a combination of 4 columns about 20 feet long, and an upper section of 12 columns 40 feet long, so that there is a total of some 140 feet in the entire plant. It has a production rate of about 4 kg per year, and the feed rates are given in Figure 1. Input is 3020 liters a day which produces about 20 liters a day of enriched material.

In new production facilities now under construction, the unit will be 720 feet high and will include nitric oxide columns.

The NO plants are somewhat more complicated (Figure 2) because ^{17}O must be separated from both ^{16}O and ^{18}O; also ^{14}N and ^{15}N are both present. A number of different combinations of columns is required. I am just giving you a rough idea of what the production facilities are like. A handout which gives much more detail about what is going on at Los Alamos is available (Los Alamos Scientific Laboratory Report, LA-4391).

What we are doing now and plan to do is probably more interesting to you.

TABLE I

ICONS PRODUCTION

kg/yr

	Now	1974
^{12}C	9	156
^{13}C	9	50
^{14}N	180	2600
^{15}N	0.7	10
^{16}O	200	3000
^{17}O	0.08	1.1
^{18}O	0.47	6.8

With such large amounts of stuff available you may wonder what we are going to do with all of it. I think I can give you a rough idea.

Some of the uses of these isotopes are shown in Table II.

TABLE II

USES

1. SNAP REACTORS
2. HEART PUMPS
3. HEART PACERS
4. ^{17}O CHEMICAL RESEARCH via. N.M.R.
5. ^{15}N HEAVY ION ACCELERATORS
6. ^{13}C CHEMICAL RESEARCH - N.M.R.
7. ^{13}C WILL REVOLUTIONIZE BIOLOGY, BIOCHEMISTRY, AND CLINICAL MEDICINE.

^{16}O is being used in SNAP reactors. Those are power reactors in which the heat produced by alpha particles is used. If human beings are working near them one must worry about the neutron background from (α,n) reactions, so they make ^{238}Pu oxide with ^{16}O which has as low a background as the metal itself. It is also used in heart pump experiments as a power source, as well as in heart pacers.

Essentially all of the ^{17}O is used at Los Alamos for NMR in physical, inorganic, and organic chemistry research. No ^{17}O from this source is available outside the laboratory. ^{15}N and ^{18}O are used in chemical research, but they are also used in heavy ion accelerators because they are rich in neutrons. ^{12}C, not listed in the table, will be used for beam dumps and making mechanical parts for accelerators. It has very low cross-sections for many accelerator reactions.

^{13}C is used in chemical research. We also think that because carbon forms the backbone of all organic molecules, it will cause a little revolution in biochemical and medical research.

TABLE III

SOME DISEASES THAT MAY BE DIAGNOSED
BY A SIMPLE ORAL FEEDING OF A SPECIAL COMPOUND OF ^{13}C
AND A BREATH ANALYSIS FOR $^{13}CO_2$

EARLY DIABETES
THYROID DISEASE
THIAMINE DEFICIENCY
STEATORRHEA
FOLIC ACID DEFICIENCY ANEMIAS
RADIATION SICKNESS
HYPER-ADRENAL GLUCOCORTICOIDISM
PELLAGRA
DIVERTICULITIS
TROPICAL SPRUE
MALABSORPTION SYNDROME
HYPERLIPEMIAS
GOUT OR HYPERURICEMIA
ARTEROSCLEROSIS
HEART DISEASE

Table III was compiled by Dr. Walton Shreeve from Brookhaven National Laboratory. He suggests a group of diseases that may be diagnosed by simple oral feeding and breath analysis for ^{13}C dioxide. In fact, there is a cooperative experiment on the diagnosis of early diabetes among Los Alamos Scientific Laboratory, Brookhaven National Laboratory, and the Argonne National Laboratory, in which Dr. Peter Klein in taking part.

With these isotopes available in large quantities, it is desirable to have simple and convenient schemes for detection. Such methodology is all-important for you who need to use them for diagnostic purposes or for tracing. Methods that are available to you, or at least some of them, are presented in Table IV.

TABLE IV

METHODS OF DETECTION

MASS SPECTROSCOPY - MOST SENSITIVE AND GENERAL METHOD. DIFFICULT WITH COMPLICATED MOLECULES.

NUCLEAR MAGNETIC RESONANCE - ODD NUCLEI ^{13}C, ^{15}N, and ^{33}S CAN "SEE" THE ENVIRONMENT OF THE ATOM IN A COMPLEX MOLECULE.

VIBRATIONAL SPECTROSCOPY - SIMPLE MOLECULES, INFRARED AND RAMAN SPECTROSCOPY.

ROTATIONAL SPECTRA - SIMPLE MOLECULES, INTERFEROMETER + FOURIER TRANSFORM

Mass spectrometry is one of the most sensitive and general methods. However, for very complex molecules it is a lot of work to get the information out in usable form.

Nuclear magnetic resonance, a newer technique, offers the advantage that you can actually see the site of the ^{13}C so that structures may be obtained, which is more difficult by other techniques. In mass spectrometry the site of ^{13}C incorporation must be found by degradation of the molecule. The odd nuclei, such as ^{17}O, ^{13}C, ^{15}N, and ^{33}S, are active in nuclear magnetic resonance.

The disadvantage of nuclear magnetic resonance is that one needs at least 10^{20} magnetic nuclei in a sample of about 2 ml, so that it requires more material than does mass spectrometry. In experiments with human beings, they being large animals, a large sample may be taken; microscopic amounts are not involved unless you are interested in substances of very low abundance.

Vibrational spectroscopy can also be used, but the sensitivity is somewhat lower. Isotope ratios may be determined to about 1.5%. In some cases, the infrared spectrometer may be capable of doing breath analyses for ^{13}C in CO_2.

H. A. Gebbe, from the Bureau of Standards at Boulder, Colorado, has developed very sensitive rotational spectrometric techniques. Samples must be converted to something that has a good rotational spectrum. Carbon dioxide will probably have to be reduced with zinc dust to carbon monoxide in order to get a decent measurement.

A type of measurement not listed in Table IV uses reactions that can be carried out at institutions where accelerators are available. Reactions like the ^{13}C (p,γ) and ^{12}C (p,γ) may be exploited. These are extremely sensitive. Isotope ratios may be obtained with as little as 10^{-9} grams of material.