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FACEPLATE

. . . the official magazine for the divers and salvors of the United States Navy

VOLUME 12, NO. 2

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TRACING NITROGEN IN DIVERS' BODIES

Mary M. Matzen
Naval Medical Research Institute

Naval Medical Research and Development Command, Work Unit No. MF85524.014.2056. The opinions and statements contained herein are the private ones of the writer and are not be be construed as official or reflecting the views of the Navy Department or Naval Service at large.

The collaboration and assistance of LCDR P.K. Weathersby, MSC, USN in the reporting of this information is gratefully acknowledged.

Development of a method for computing safer decompression schedules for Navy divers is a major mission of the Hyperbaric Medicine Program Center at the Naval Medical Research Institute (NMRI) in Bethesda, Maryland.

To improve air decompression schedules, diving researchers need a better understanding of nitrogen uptake and elimination in the human body.

As part of a study of nitrogen exchange, NMRI researchers combined their expertise with that of researchers at the Lawrence Livermore Laboratory (Livermore, California) of the University of California in the fall of 1980. The purpose of the experiment was directly to measure where and how fast nitrogen enters a diver's body. The protocol required that the subjects breathe trace amounts of radioactive nitrogen.

Personnel and Rationale

Designers of the experiment were LCDR P. K. Weathersby, MSC, USN, Dr. L. D. Homer and CAPT E. T. Flynn, MC, USN, of NMRI, and physicist P. Meyer of the Livermore Laboratory. The subjects were investigators and divers from NMRI: CAPT LCDR , HCMS(DV) , HM1(DV) , HT1(DV) , HT1(DV) and ET2(DV) .

The subjects were highly motivated, yet a bit apprehensive about the radiation exposure. Divers are accustomed to taking big risks in their work—they have been trained and are knowledgeable and competent in the hazardous diving environment. Breathing radioactive gas was a novel experience for all, but a source of particular concern to LCDR Weathersby and CAPT Flynn, whose role was to ensure that the procedures were safe.

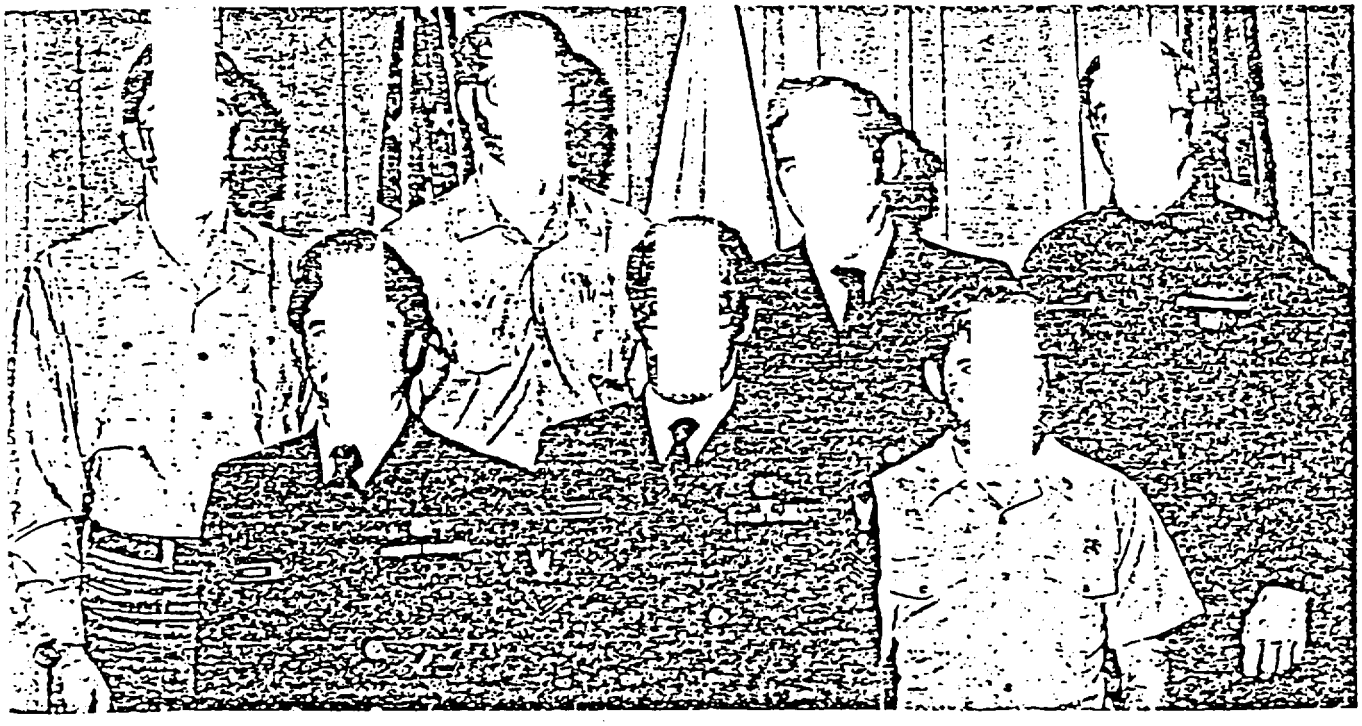

Figure 1: Subjects and investigators participating in the experiment from NMRI: front row, l-r: ET2(DV) , HT1(DV) , and HCMS(DV) ; back row, l-r: HM1(DV) , HT1(DV) , LCDR and CAPT

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Most divers have at some time suffered decompression sickness (bends), resulting from bubbles formed in the tissues after rapid decompression. The offending bubbles are assumed to be caused by the inert gas in the diver's breathing mixture. The rationale around which most decompression schedules have been developed assumed that, under increased pressure, the diver's body absorbs excess nitrogen and that this excess nitrogen generates bubbles that form in the blood stream if the pressure is rapidly reduced. Adequate decompression schedules allow the excess nitrogen to be exhaled; thus inhibiting bubble formation and preventing the occurrence of decompression sickness. *The crux of the problem is to define exactly how fast inhaled nitrogen enters and leaves parts of the diver's body.*

Experimental Procedures

Previously, medical researchers have had to approximate the tissue uptake and elimination rates of nitrogen. To get a more accurate picture of nitrogen exchange in the body, researchers have had to use other gases which are more easily detected in the body (such as radioactive Xe 133) and assume that these gases behaved like nitrogen. The few experiments that attempted to measure gas uptake and elimination have generally used anesthetized animal subjects and have used a short measuring time, such as 30 minutes. More importantly, gas exchange in a particular region of the body has not been studied because the techniques measured either expired gas or venous blood samples that contained mixtures of gas from all organs in the body. NMRI investigators sought to eliminate many of the assumptions which have to be made in these types of experiments by trying to measure nitrogen exchange directly in humans.

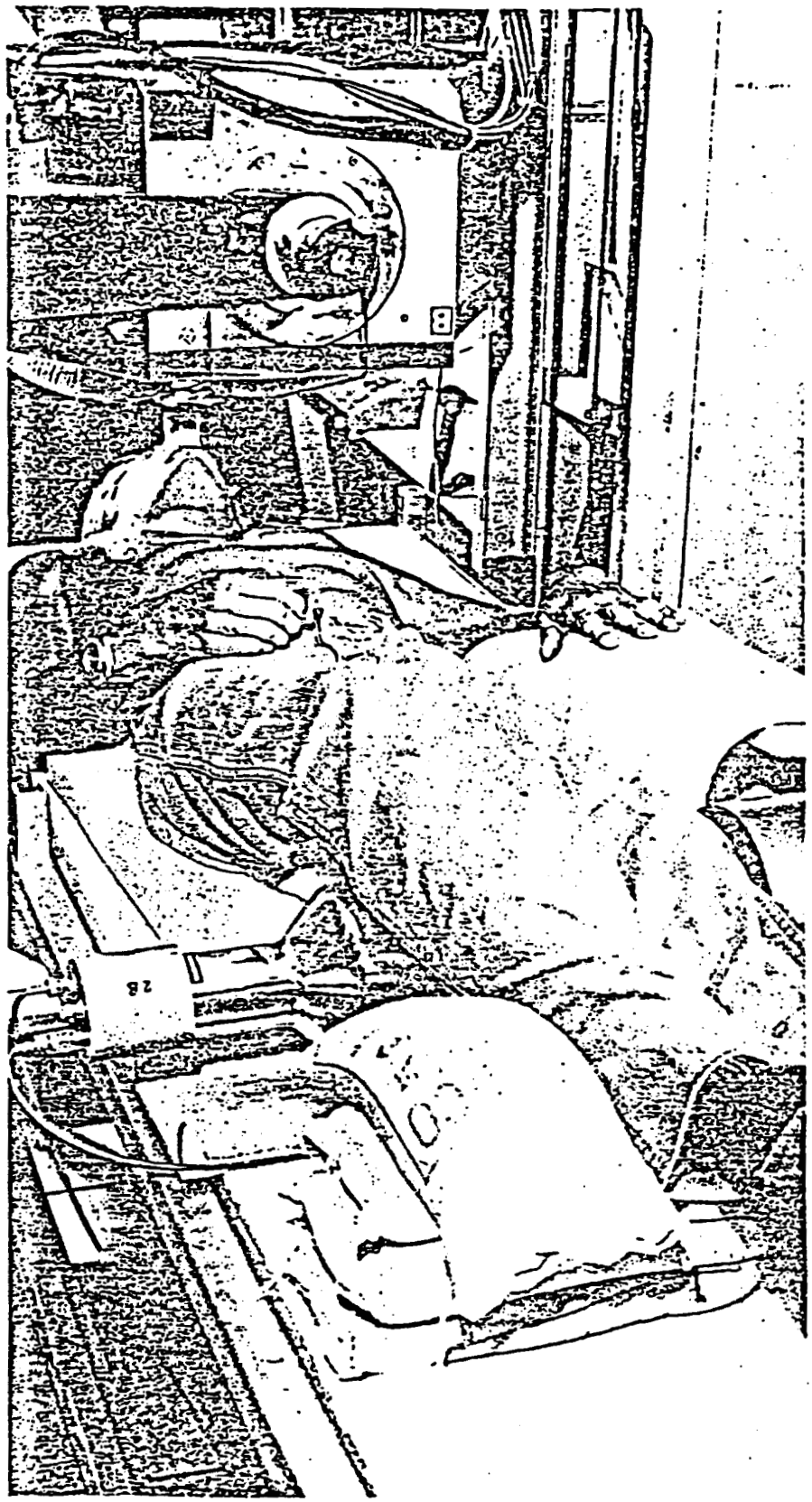

Figure 4: One of the subjects in position for the experiment. Mouthpiece is connected to the $^{13}N_2$ rebreathing bag in another location in the room. The hexagonal structure above the subject is one of the two heads of the positron camera (the second is out of view below the table). A separate pair of positron detectors is in place around the subject's left knee.

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Nitrogen is hard to measure. It has no color and no odor. It has no optical, electrical, magnetic, or nuclear properties that make it easy to identify. In the Livermore experiment, the subjects breathed a mixture of 20 percent oxygen and 80 percent nitrogen that included a small fraction of radioactive nitrogen ($^{13}N_2$). This nitrogen, which behaves chemically the same as normal $^{14}N_2$, could be traced anywhere in the subjects' bodies.

Physicist Paul Meyer has assembled the equipment and expertise that makes the Livermore Laboratory one of the few sites in the world where $^{13}N_2$ can be produced and studied in humans. The nitrogen for this experiment was prepared on-site because $^{13}N_2$ has a radiologic half-time of only 10 minutes. This means that a 1-hour delay in transporting would reduce the amount of radioactive gas by 98 percent. The $^{13}N_2$ is prepared by bombarding pure nitrogen with gamma rays (see explanation in Figures 2 and 3). This procedure was accomplished by remote control in a well-sealed accelerator area. Intensity of the rays was such that 1/300 second of exposure to the direct beam would be fatal. To get sufficiently "hot" nitrogen to serve as an effective tracer, a 50-minute irradiation time was required. A danger inherent in the procedure was the chemical risk that could arise from the possible creation of noxious gases during preparation of the radioactive nitrogen. However, gas monitoring showed that creation of such gases did not occur.

An unavoidable risk in this experiment was exposure of the subjects to ionizing radiation as they breathed the $^{13}N_2$ mixture. In fact, a major part of the researchers' time was spent in designing and monitoring the experimental procedures to keep the exposure at an acceptably low level.

During the 30 minutes that the subjects breathed the radioactive gas (at 1 atmosphere in these first experiments) and for up to 90 minutes thereafter, the location of the $^{13}N_2$ was identified and measured in their bodies as they lay inside a radiation device known as a positron gamma camera (Figure 4). The areas in the body of special interest were those most often affected by decompression "hits": the shoulder, knee and inner ear.

In ideal circumstances, the information (image) obtained from a positron camera is three-dimensional in nature. However, these experiments were limited by the maximum specified radiation dose to each subject. The "mere" 500,000 or so radioactive disintegrations recorded for each subject do not provide a perfect reconstruction of the "image." Extensive computer programming and operation are needed to "crunch" (or assimilate) the data points into a useful form such as shown in Figure 5. The data should provide estimates of comparative nitrogen capacity in the shoulder, knee and inner ear, as well as the average time and variations in the amount of time that nitrogen stayed in these areas.

Results

This long overdue and important study will provide real information about the way air behaves in the diver's body. NMRI researchers who are attempting to devise a better model for computing air decompression tables await this vital information. Conclusions can't be drawn until the data is analyzed; but the results of the experiment could change old theories or add new ones.

Comment

On a lighter note: The diver subjects reported disappointment that Livermore was not a bustling naval port. Their disappointment was offset, however, when they found the local winery was suitable for an occasional "culturally inspiring" visit—an activity dear to a diver's heart.

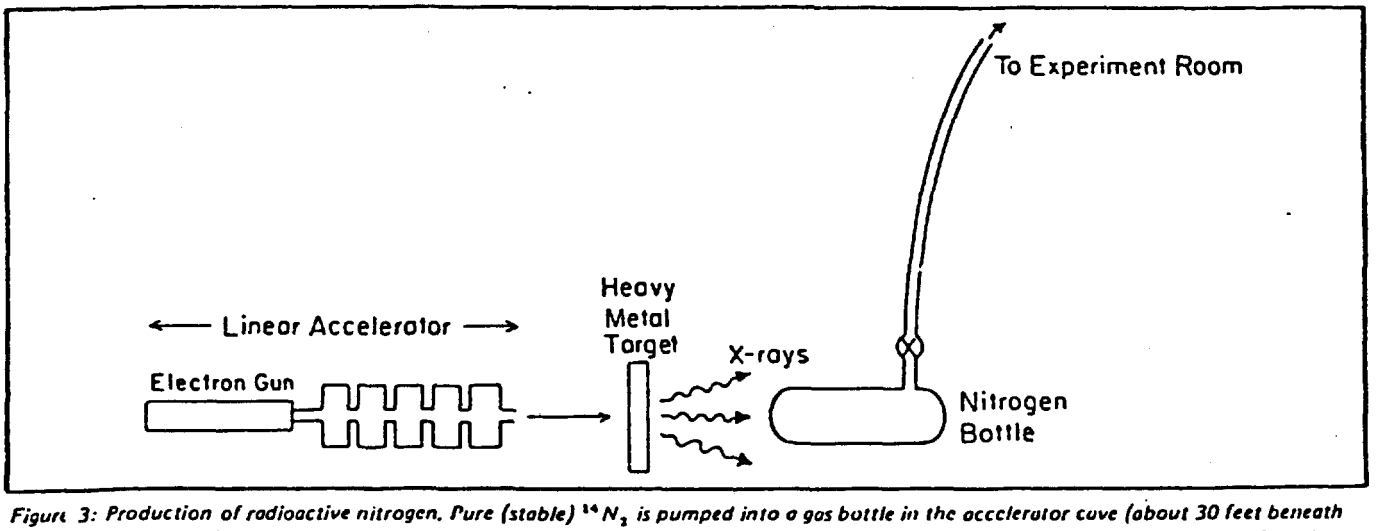

Figure 3: Production of radioactive nitrogen. Pure (stable) $^{14}N_2$ is pumped into a gas bottle in the accelerator cave (about 30 feet beneath the experiment room). Electrons are produced and accelerated to nearly the speed of light and to over 50 times their rest mass before they are scattered and their energy converted to X rays ("Bremsstrahlung"). The X rays bombard the nitrogen bottle and cause the nuclear reaction that produces radioactive $^{13}N_2$.

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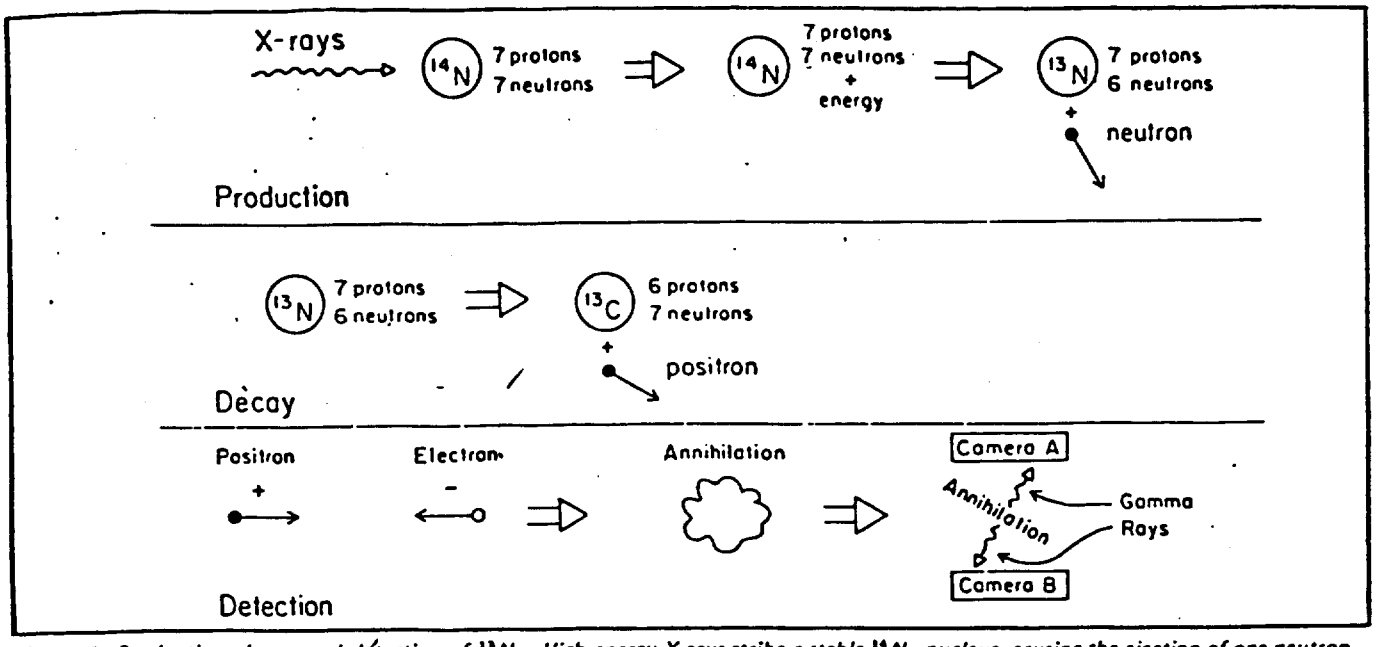

Figure 2: Production, decay, and detection of $^{13}N_2$. High energy X rays strike a stable $^{14}N_2$ nucleus, causing the ejection of one neutron to produce the radioactive isotope $^{13}N_2$. Within an average of 14 minutes the unstable $^{13}N_2$ decays to eject a positron—an electron with a positive charge. Because the positron is the corresponding anti-matter particle to the electron, it soon interacts with an electron, and both are annihilated. The positron and electron masses are converted into energy in the form of two gamma rays emitted in opposite directions. When their direction of travel causes both to hit the faces of the two gamma cameras, the location and time of the annihilation is recorded as one data point.

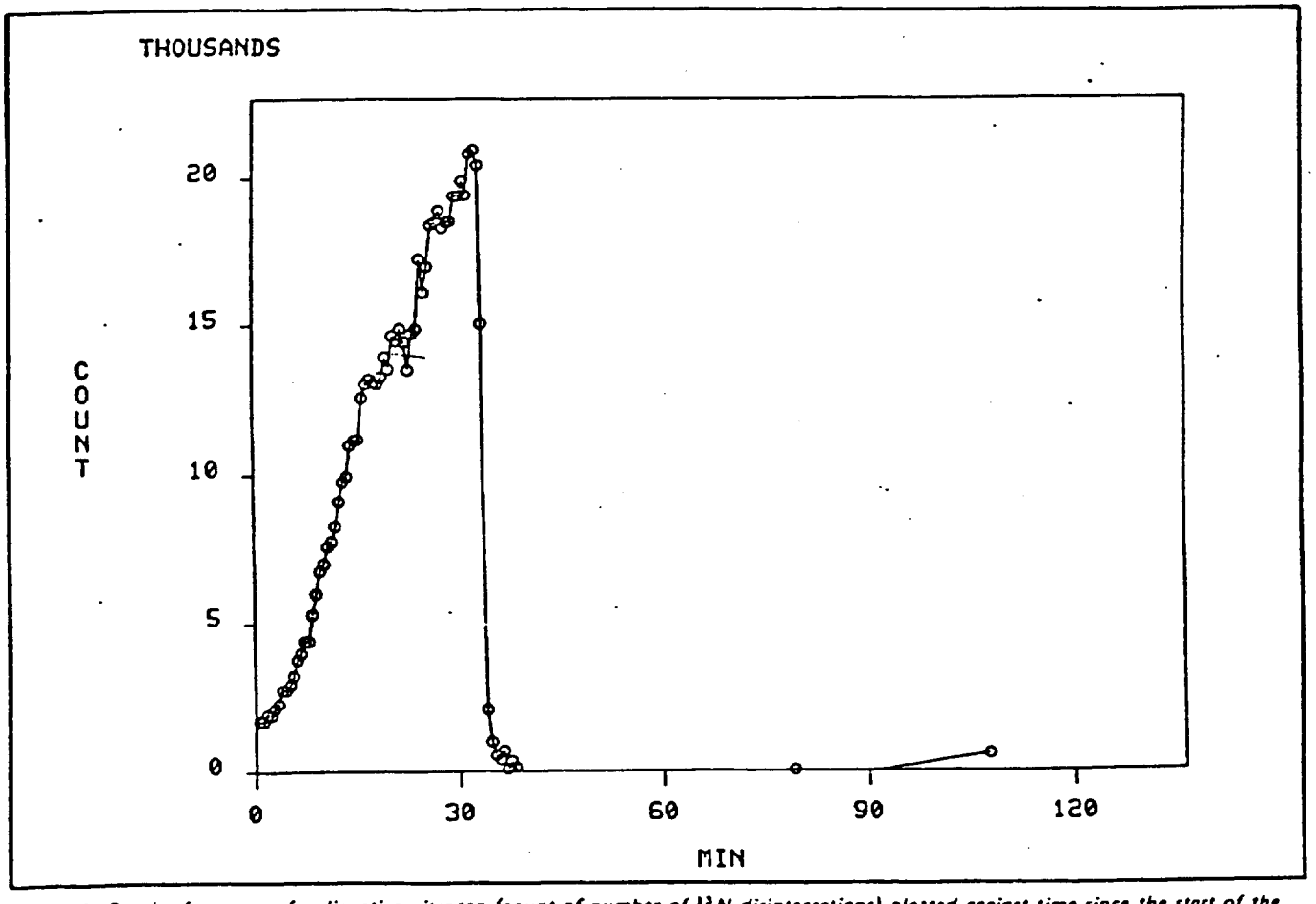

Figure 5: Graph of amount of radioactive nitrogen (count of number of ^{13}N disintegrations) plotted against time since the start of the experiment. This information was obtained from the shoulder of one of the NMRI subjects and has been corrected for the radiologic half time of ^{13}N. The sharp fall at 30 minutes followed the switch from inspiring the $^{13}N_2$ mixture to inspiring room air.

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HUMAN SUBJECT EXPERIMENTS WITH AIR TAGGED WITH RADIOISOTOPES ^{13}N and ^{41}Ar

PREFACE

The Laboratory's basic safety policy is that operations must be planned and conducted in a manner that will prevent injury to personnel or damage to property. The minimum safety rules and practices necessary for achieving an accident-free work environment for the human subject experiments with air tagged with radioisotopes in Building 194 are stated in the Operational Safety Procedure.

Everyone in this building, i.e., visitor, maintenance and service employee, and regularly assigned employee, is required to abide by this procedure and the LLNL Health & Safety Manual to protect himself and other personnel from injury. Regular building personnel are responsible for assisting others in the building to understand the safety regulations relating to what they are doing and to abide by the safety requirements.

This procedure was prepared by building management assisted by Hazards Control. Confer with the Hazards Control safety team assigned to this building for interpretation of this procedure and for planning your operations to comply with safety requirements. Each individual in this building shall use this guidance effectively to avoid injury.

This Operational Safety Procedure has been reviewed by:

R. W. Bauer	E. Division
A. J. Toy	Hazards Control
D. C. Shepherd	Human Subject Committee

This Operational Safety Procedure is approved by:

John D. Anderson
Associate Director
for Physics

HUMAN SUBJECT EXPERIMENTS WITH AIR TAGGED WITH RADIOISOTOPES ^{13}N and ^{41}Ar

A. INTRODUCTION:

1. General

The purpose of this study is to measure the rate of nitrogen and Argon uptake and elimination in the body of normal healthy humans. The experiments will involve breathing of ^{13}N and ^{41}Ar labelled air for no more than 120 minutes.

2. Changes

Any required change in operations that alters the scope or significantly decreases safety control will not be made until a revision or supplement to this procedure has been signed by the person authorized to approve this OSP. Any required change in operations that does not decrease the safety control may be made with the joint concurrence of the LINAC Operations Manager and the Hazards Control Safety Team Leader.

B. SCOPE

1. This procedure authorizes the exposure of human subjects to the following:

   a) Breathing of air tagged with ^{13}N and ^{41}Ar for up to 120 minutes.

C. HAZARDS ANALYSIS:

1. Radiation Hazard

Estimates of the radiation dose from ^{13}N and ^{41}Ar activities in the breathing mixture are based on calculations by Hazards Control's Health Physics Group (see letter from K. Shingleton of April 12, 1982). The dose per mCi per liter for ^{13}N is ~ 1000 mr and for ^{41}Ar: 6400 mr. To obtain extimates of the expected dose we take the gas mixes and decay activities into account as seen below:

^{13}N-activity at t=o (beam shut-off) = 1.8 mCi/liter
^{41}Ar activity at t=o (beam shut-off) = 0.001 mCi/liter

The breathing gas concentrations will be:

$*N_2$ (80%) + O_2 (20%) or $*N_2$ (75%) + *Ar (5%) + O_2 (20%)

Half lives ($T_{1/2}$) for the isotopes are ^{13}N: 10 min. and ^{41}AR: 109 min. Time elapsed from beam shut-off to administration will be ~ 20 minutes. With this in mind we obtain the estimates at t=20 min. for 120 minute exposure.

Total dose = (~~dose~~ dose/mCi/ℓ) (concentration)(activity) ($e^{-\lambda t}$)
$*N_2 + O_2$: (1000) (0.80) (1.8) (0.25) = 360 mr
$*Ar + *N_2 + O_2$: (6400) (0.05) (0.001) (0.881) + (1000) (0.75) (1.8) (0.25)
= 0.26 + 337.5 = 338 mr
revised 344

2. Gas Hazards (NO_2)

To generate the ^{13}N isotope, high-purity N_2 is irradiated with bremsstrahlung. Some trace of O_2 always is present and in this ionizing environment, NO_2 and N_2O forms. The concentration is controlled by minimizing the presence of O_2 in the nitrogen.

The Operational Controls in paragraph F will reduce the above hazards to an acceptable level.

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D. RESPONSIBILITIES:

1. Supervisor

Paul Meyer is responsible for assuring that all work is performed in conformance with this OSP and the LLNL Health & Safety Manual. In his absence, the experiment will be terminated and a responsible person will be trained for the experiment.

2. Employee

All participating employees are responsible for performing their work according to the regulations of this OSP. They are expected to take all reasonable precautions to protect themselves and their fellow employees and to perform only those tasks that they believe can be accomplished safely. When participants have any doubt regarding the safety of any phase of their work, they are expected to check with the project supervisor before proceeding.

3. Hazards Control

The Hazards Control Safety Team assists management to institute and to maintain a low-risk work environment. In addition, Hazards Control may request that management or employees stop an operation when there appears to be an imminent danger to personnel or property (see Health & Safety Manual Section 1.06).

E. MATERIAL CONTROLS:

1. The target gases are:

a) AR: Zero grade

b) N_2: High purity nitrogen (silver colored bottles with pink top).

2. Waste gas disposal is achieved with large volumn blower which pumps gas from the site of the experiment to the outside of Bldg. 194 at the roof level.

F. OPERATIONAL CONTROLS:

1. All human subjects shall receive a whole body radiation scan by Hazards Control before and after inhalation of radioactive gases.

2. The radioactive gases shall be filtered with a HEPA filter before inhalation by the subjects. A visual inspection of the filter cartridge gaskets and canister will be made prior to filter installation. Only an approved and tested filter cartridge obtained from Hazards Control Respirator Service will be installed in the filter canister.

3. Radioactive gas preparation:

The evacuated target gas bottle, located in the 0^0 cave, is filled from a standard gas cylinder containing either high-purity nitrogen (N_2) or Zero grade Ar. Upon filling, the gas is being irradiated by LINAC bremsstrahlung.

In the case of N_2 as target gas, any undesired by-products come from small oxygen concentrations in the gas bottle. This can lead, in principle, to NO_2 and N_2O. Tests performed previously by Hazards Control personnel, found concentrations of less than 1 ppm of NO_2 and less than 22 ppm of N_2O in an irradiated sample. The breathing mixture will be tested for NO_2 and ozone before it is administered.

G. PROCEDURE

a) Evacuate target-gas bottle in 0^2 cave to $\leq$ 50 microns.

b) Fill target bottle with N_2 or N_2 + ^{40}Ar.

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c) Bleed radioactive gas as described below, into plastic bag.

d) Check mixture for NO_2 (≤ 5 ppm).

e) Mix active N_2 with clean O_2 to 4 parts $*N_2$ and 1 part O_2 in plastic bag.

f) Navy personnel will continuously monitor and hold O_2 concentration to approximately 20%.

Exposure Procedure

$*N_2$ or $*N_2$ + *Ar

The prepared and tested gas mixture is taken from Trailer 930 to the subject in Bldg. 194 in a plastic bag which is then connected to the breathing valve. The subject then breathes for 120 minutes from the bag. The exhaled gas is passed through a soda lime trap to remove all Co_2 before returning to the bag. A concentration of ~20% O_2 is maintained in the bag and monitored with a bio-marine oxygen deficiency meter or equivalent during use by Navy personnel. At the end of the 120 minute period the bag is disconnected and the subject breathes room air with the washout being vented to the outside of Bldg. 194.

Distribution:
Alvarez, R.
Anderson, J. D.
Bauer, R. W.
Burgin, C.
Clatworthy, J.
Costella, G.
Eneidi, W. (5)
Johnson, J. S.
Meyer, P.
Olsen, J. L.
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Shingleton, K.
White, R.
Fire Safety Group (B)

GENERAL SERVICES ADMINISTRATION AND
INTERAGENCY COMMITTEE ON MEDICAL RECORDS
FPMR 101-11.406-8
OCTOBER 1975

Research Work Unit:63713N.M0099PN.01A

CLINICAL RECORD	NARRATIVE SUMMARY	
DATE OF ADMISSION	DATE OF DISCHARGE	NUMBER OF DAYS HOSPITALIZED
-NA-	-NA-	-NA-

(Sign and date at end of narrative)

On 5 May 1982, after signing informed consent, this individual was a test subject in a joint Naval Medical Research Institute and Lawrence Livermore Laboratory experiment. He breathed a normoxic mixture of N_2, Ar, and O_2 from a recirculation system containing the radioisotopes N-13 (positron emitter, $T\frac{1}{2}$=10min.) and Ar-41 (beta and gamma emitter, $T\frac{1}{2}$=110min.). The isotopes were simultaneously produced in an accelerator to a specific activity of 0.88 mCi/L of N-13 and 0.030 mCi/L of Ar-41. Less than 0.00001 mCi/L of Ar-39 was also produced but would contribute a negligble dose. During a 20 min. period (N-13 decay to 0.22 mCi/L), the activated gas was analyzed (O_3<0.3ppm, NO_2<5ppm) and 50/L of it was mixed with 12.5/L of O_2 and then 20/L of room air (dilution factor of 50/82.5=0.61). The experiment consisted of 120 min. quiet breathing of the gas mixture, maintained normoxic, while the subject was studied with gamma detectors.

The only risk expected from the experiment was the exposure to ionizing radiation. Externally worn dosimeters recorded <10 mrad; a whole body count showed only normal amounts of K40 after the experiment. Calculated internal exposures were under 5 mrad to non-lung tissues including gonads; 136 mrad to trachea with large airways expected to be lower; and 160 mrad to the lungs. Exposure calculations are given below:

$$\text{Dose} = SA(mCi/L)\ Te(min)\ [V(L)/M(g)]\ E(MeV/dis)\ K(35500\ mrad\text{-}g/mCi\text{-}min)$$

SA is maximum inspired specific activity as given above, Te is effective exposure time, E is energy per disintegration, V is organ volume of distribution, M is organ mass, and K is a radiologic constant:

$$K = (3.7\times10^{7}\ dis/sec\text{-}mCi)(60\ sec/min)(1.6\times10^{-6}\ erg/MeV)/(0.1\ erg/g\text{-}mrad)$$

For time calculations, lung and trachea were assumed to equilibrate instantly, while internal organs were assumed to follow exponential exchange kinetics. (Biological time constant (Tb) equals tissue-blood partition coefficient divided by specific blood flow rate). The Tb was used together with the radiological decay time constant ($T\frac{1}{2}$/.693) in an integration over both uptake and elimination phases to produce a single effective organ exposure time (Te) for use with initial exposure rate. Energy deposited in tissue per disintegration (E) was obtained by adding average beta and positron energy (all tissues) plus gamma (including annihilation photons) energy absorption through 10 cm of 0.25 g/ml tissue (lung) or 1 cm of 1.0 g/ml tissue (marrow and gonad). Organ volume (V) and mass (M) were obtained by measured supine mid-tidal lung volume (FRC+.5V_T) and assumed lung mass of 1000 g: assumed volume of 30/ml and assumed mass

(Continued)

(Use additional sheets of this form (Standard Form 502) if more space is required)

SIGNATURE OF PHYSICIAN	DATE	IDENTIFICATION NO.	ORGANIZATION
			NMRI, Bethesda, MD

PATIENT'S IDENTIFICATION (For typed or written entries give: Name - last, first, middle; grade; date; hospital or medical facility)	REGISTER NO.	WARD NO.
Research Work Unit:63713N.M0099PN.01A		

[redacted]
HM2/AD/USN

NARRATIVE SUMMARY
Standard Form 502
502-112

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Research Work Unit:63710N.M0099PN.01A

CLINICAL RECORD	NARRATIVE SUMMARY	
DATE OF ADMISSION	DATE OF DISCHARGE	NUMBER OF DAYS HOSPITALIZED
-NA-	-NA-	-NA-

(Sign and date at end of narrative)

of 13.6 g for trachea; and assumed density of 1.0 for gonad and marrow with tissue/gas partition coefficients of 0.02 in gonad and 0.05 in marrow.

Tissue		SA(mCi/L)	E(MeV)	V/M(L/g)	Tb(min)	Te(min)	Dose(mrad)
Lung	N-13	0.134	0.574	2.3/1000	<1	14.4	91
	Ar-41	0.0183	0.550	"	"	83.9	69
Trachea	N-13	0.134	0.500	.03/13.6	"	14.4	81
	Ar-41	0.0183	0.462	"	"	83.9	55
Gonad	N-13	0.134	0.530	0.00002	17	6.6	0.3
	Ar-41	0.0183	0.498	"	"	70	0.5
Marrow	N-13	0.134	0.530	0.00005	6.6	10	1.3
	Ar-41	0.0183	0.498	0.00005	"	78	1.3

P. K. WEATHERSBY
LCDR, MSC, USN

E. T. FLYNN, Jr.
CAPT., MC, USN

(Use additional sheets of this form (Standard Form 502) if more space is required)

SIGNATURE OF PHYSICIAN	DATE	IDENTIFICATION NO	ORGANIZATION
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PATIENT'S IDENTIFICATION (For typed or written entries give: Name - last, first, middle, grade; date; hospital or medical facility)	REGISTER NO.	WARD NO.
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