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July 5, 1984

TO: Frederick T. Hatch, Chairman Human Subjects Committee

FROM: Paul Meyer

SUBJECT: Renewal of Human Subjects Approval 80P-109-02

The purpose of the work proposed is to measure the rate of uptake and elimination of nitrogen and argon in the body of normal, healthy humans. Experiments will involve breathing of $^{13}N$ and $^{41}Ar$ labelled air for up to two hours at an initial specific activity of up to $\sim 1\ \mu$ Ci per liter of $^{13}N$ and 24 $\mu$ Ci per liter of $^{41}Ar$. P. K. Weathersby, CDR, MSC, USN, is the principal investigator and E. T. Flynn, Jr., Capt., MC, USN and myself are associate investigators. All test subjects will be Navy personnel volunteers. The protocol for the proposed experiments is identical to that followed in 1982 and an Operating Safety Procedure renewal is presently being processed by Hazards Control. Calculated radiation exposures are as indicated in an enclosed clinical record of a 1982 test subject. Experiments are scheduled for September 1984 and funding is provided by the Naval Medical Research Institute in Bethesda, MD. I would appreciate your written approval before September of this year.

PM/pld 0595m/0038m

Encl.: Background material: Navy Publication
OSP No. 194.27, expired 4/20/83
clinical record of 1982 test subject

REPOSITORY LLNL B361, Rm. B940A
COLLECTION Institutional Review Board
BOX No IRB Protocol File
FOLDER Meyer, P. IRM No. 80P-109
Decompression Sickness Studies
with Radioactive Gases
Folder 1 of 2

University of California
LAWRENCE LIVERMORE LABORATORY

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VOLUME 12, NO. 2

# FACEPLATE

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PRIVACY ACT MATERIAL REMOVED

# 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.

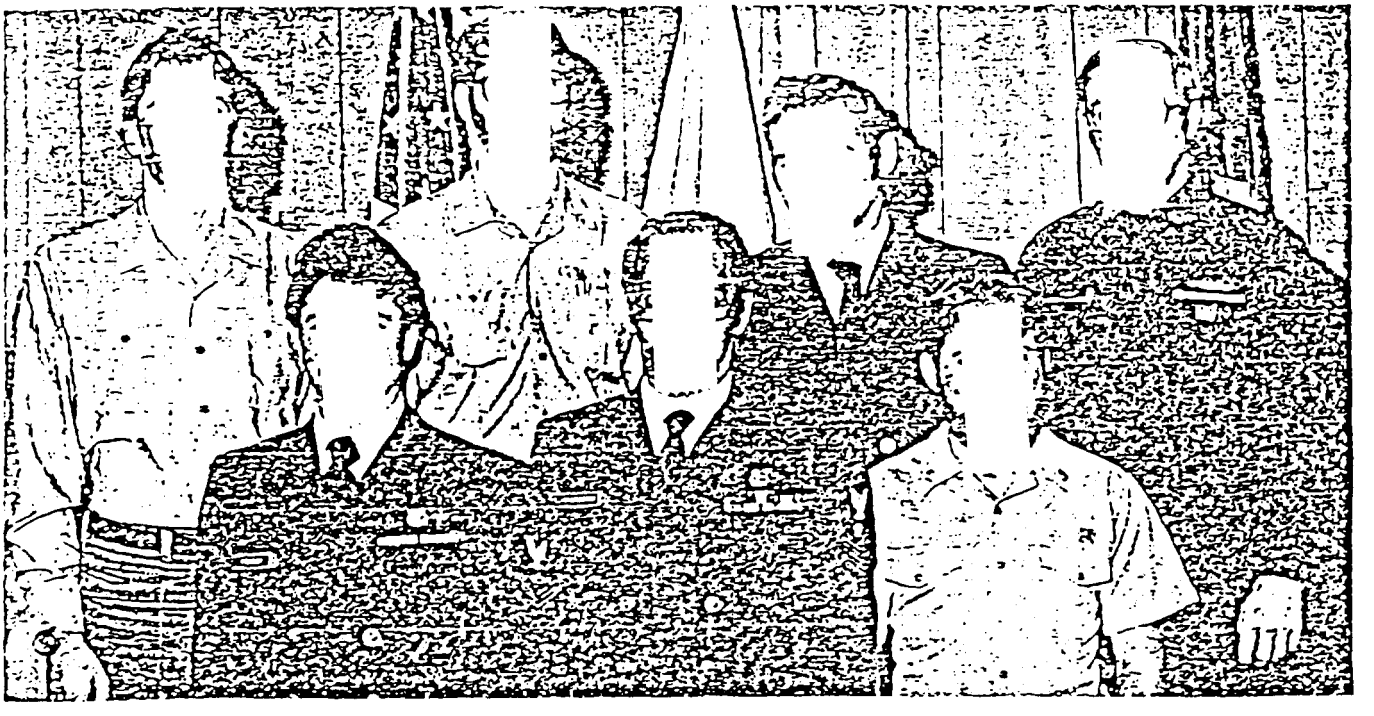

*Figure 1: Subjects and investigators participating in the experiment from NMRI: front row, l-r: ET2(DV) , HT1(DV) , and HCMS(DV) ; back row, l-r: HM1(DV) , HT1(DV) , LCDR , and CAPT*



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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.

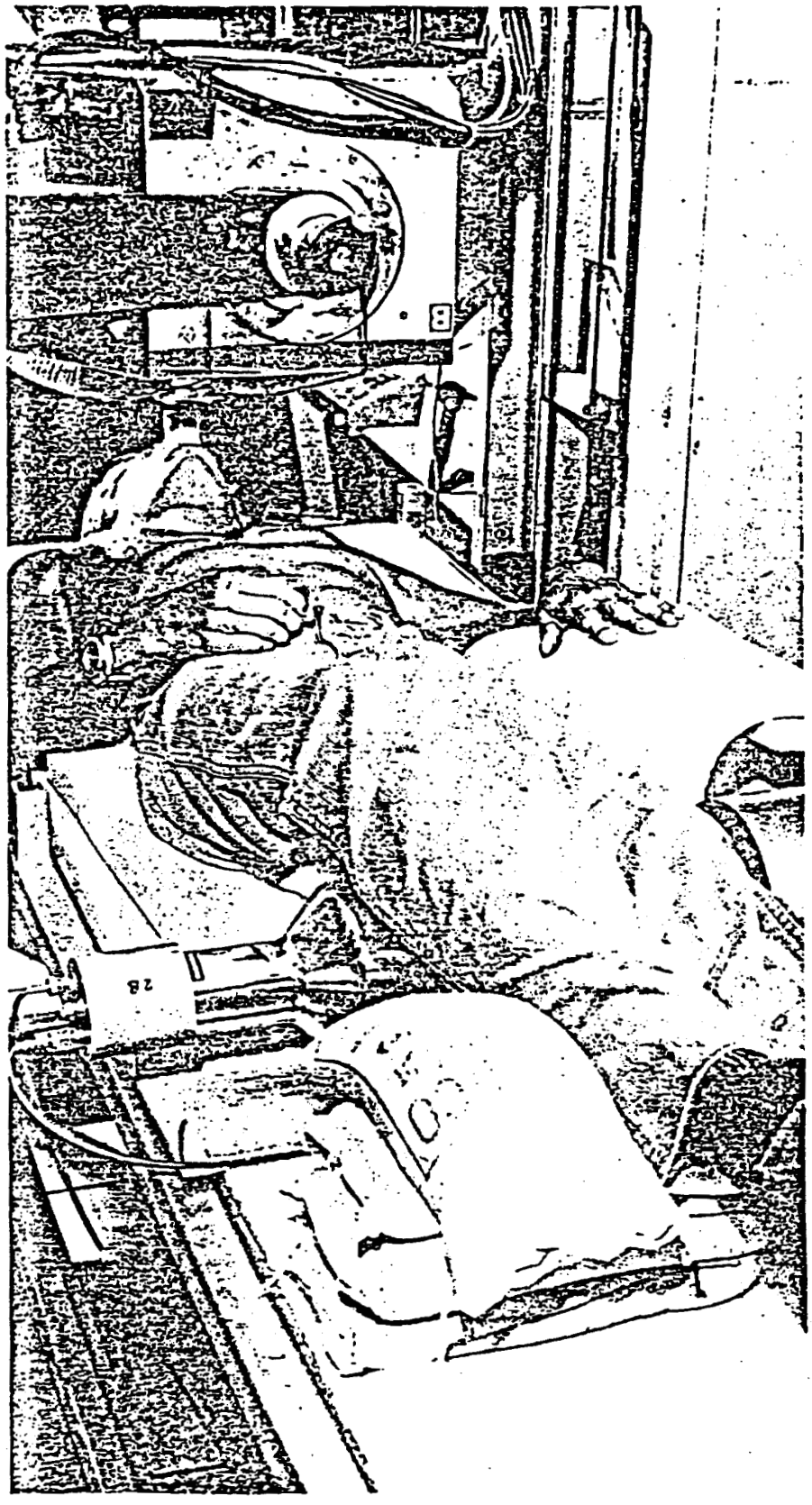

*Figure 4: One of the subjects in position for the experiment. Mouthpiece is connected to the $^{13}N_2$ rebreathing bag in another location in the room. The hexagonal structure above the subject is one of the two heads of the positron camera (the second is out of view below the table). A separate pair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

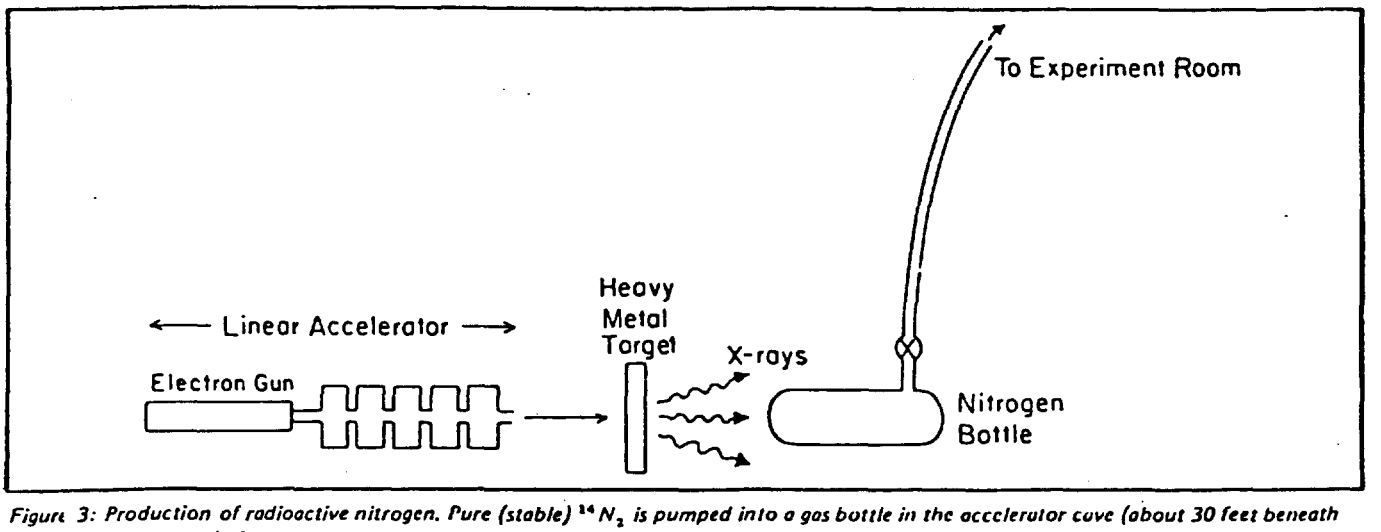


*Figure 3: Production of radioactive nitrogen. Pure (stable) $^{14}N_2$ is pumped into a gas bottle in the accelerator cave (about 30 feet beneath the experiment room). Electrons are produced and accelerated to nearly the speed of light and to over 50 times their rest mass before they are scattered and 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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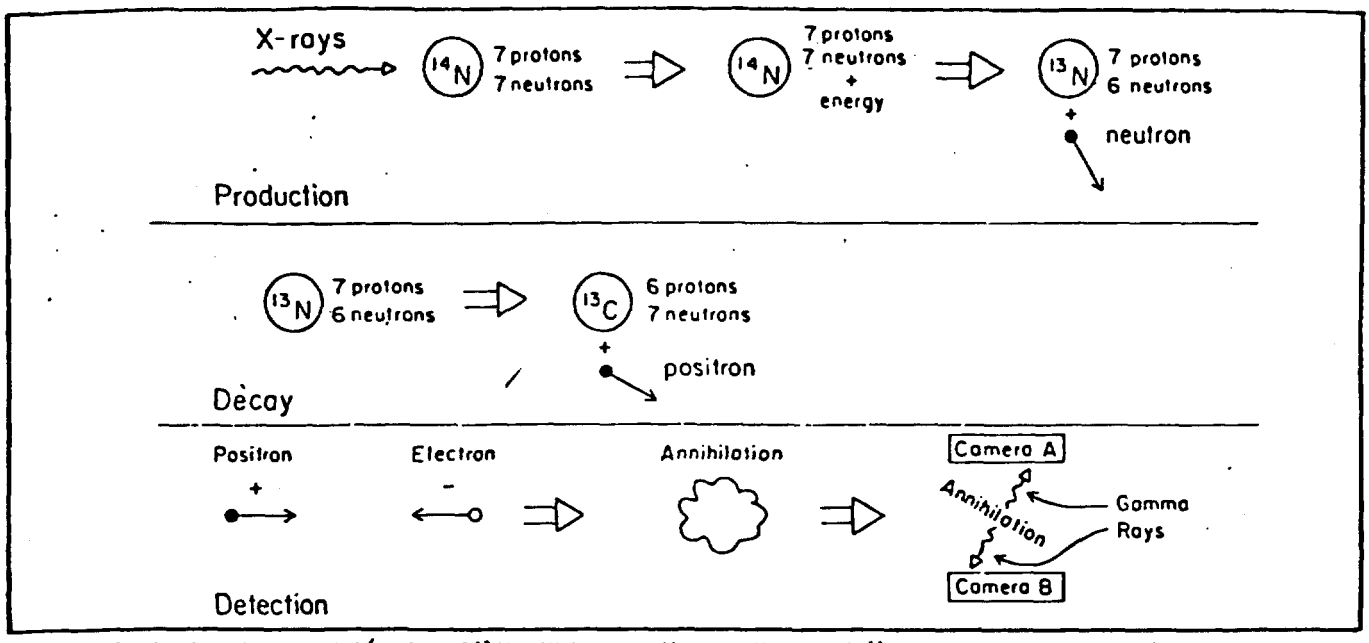


*Figure 2: Production, decay, and detection of $^{13}N_2$. High energy X rays strike a stable $^{14}N_2$ nucleus, causing the ejection of one neutron to produce the radioactive isotope $^{13}N_2$. Within an average of 14 minutes the unstable $^{13}N_2$ decays to eject a positron—an electron with a positive 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.*

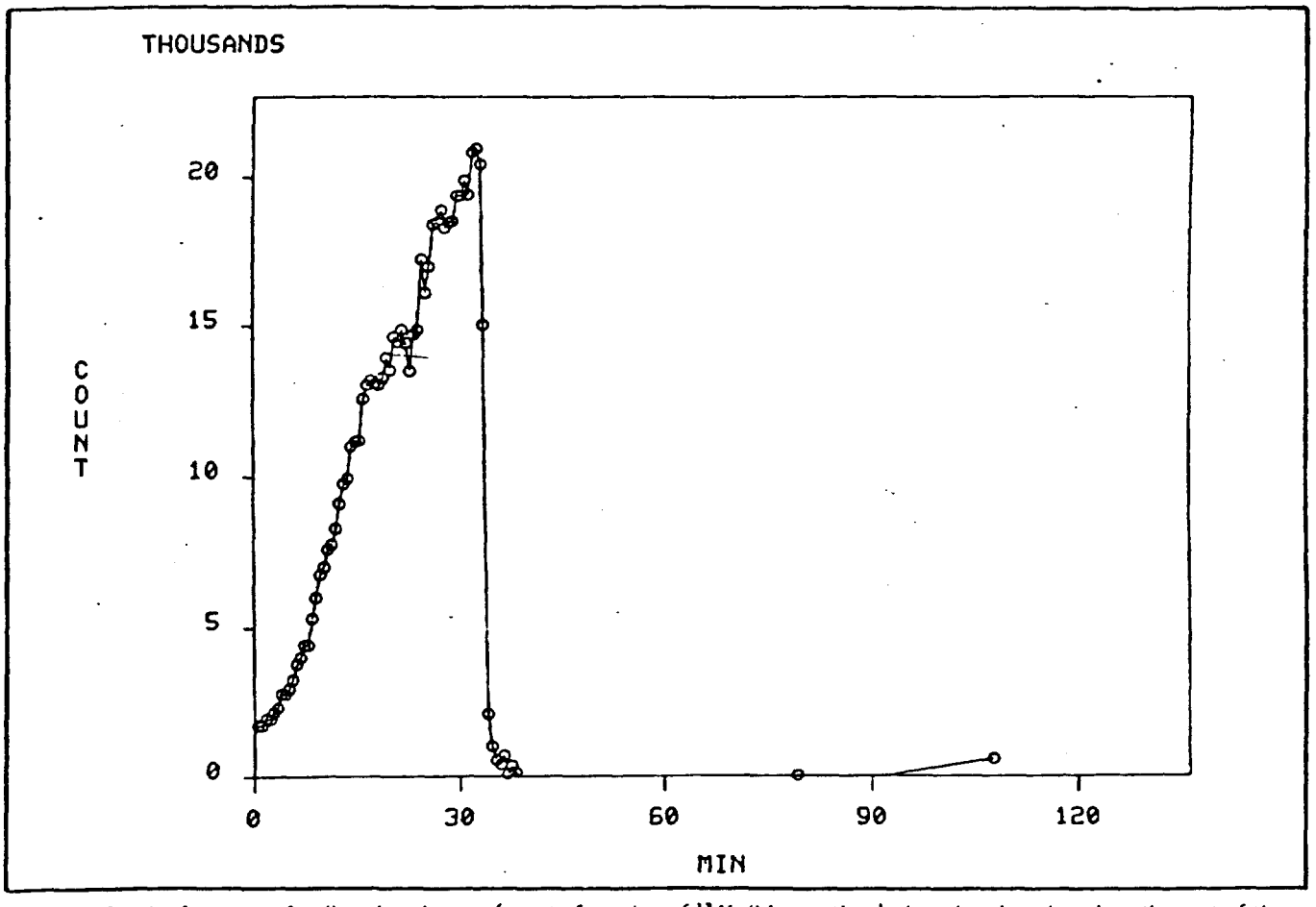


*Figure 5: Graph of amount of radioactive nitrogen (count of number of $^{13}N$ disintegrations) plotted against time since the start of the experiment. This information was obtained from the shoulder of one of the NMRI subjects and has been corrected for the radiologic half time of $^{13}N$. The sharp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



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