Hyperpolarized MRI with polarized He3 gas

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Collaborators

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G. Frossati	*Leiden/ Netherlands*
J. P. Didelez	*IPN/Orsay/ France*

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1.Introduction

1.1. When and why did the ^{3}He-MRI get started?

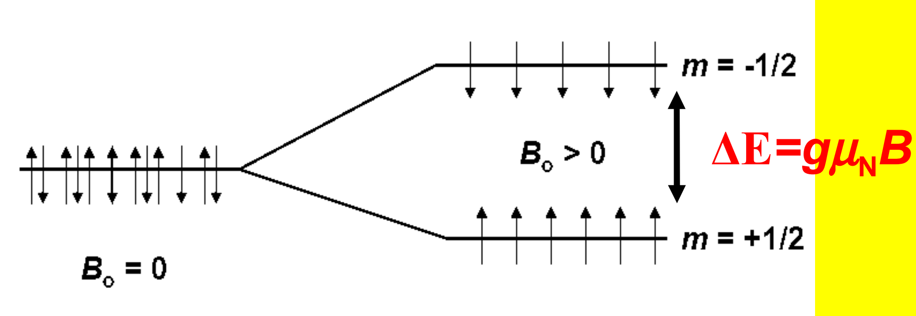
- ☐ Since the late 1970s,W. Happer (Princeton) had been investigating spin-exchange optical pumping as a means of polarizing nuclei with thought to practical things one might do with large collections of nuclei thus polarized.
- ☐ Among them, they are the enhancement of fusion in tokamaks, the creation of new kinds of polarized targets for high-energy physics, and the improvement of clinical magnetic resonance imaging.
- ☐ In 1991, when he stayed in Washington as a director of DOE, he ruptured a disk and an MRI scanning was done for his spines.
- ☐ Since he was in great pain, and that concentrated his mind wonderfully.
- ☐ Thus began the effort by W. Happer, G. Cates and collaborators to do clinical magnetic resonance imaging with noble gases.
- ☐ In 1994, W. Happer’s Princeton group, working with colleagues at the Univ. of New York, Stony Brook published MRI images of the excised heart and lungs of a mouse made with nuclear polarized ^{129}Xe.

1.2. Why is highly polarized ³He gas needed for MRI?

Polarization in thermal equilibrium

$$H = -\mu \cdot B = -g\mu_N I_z B$$

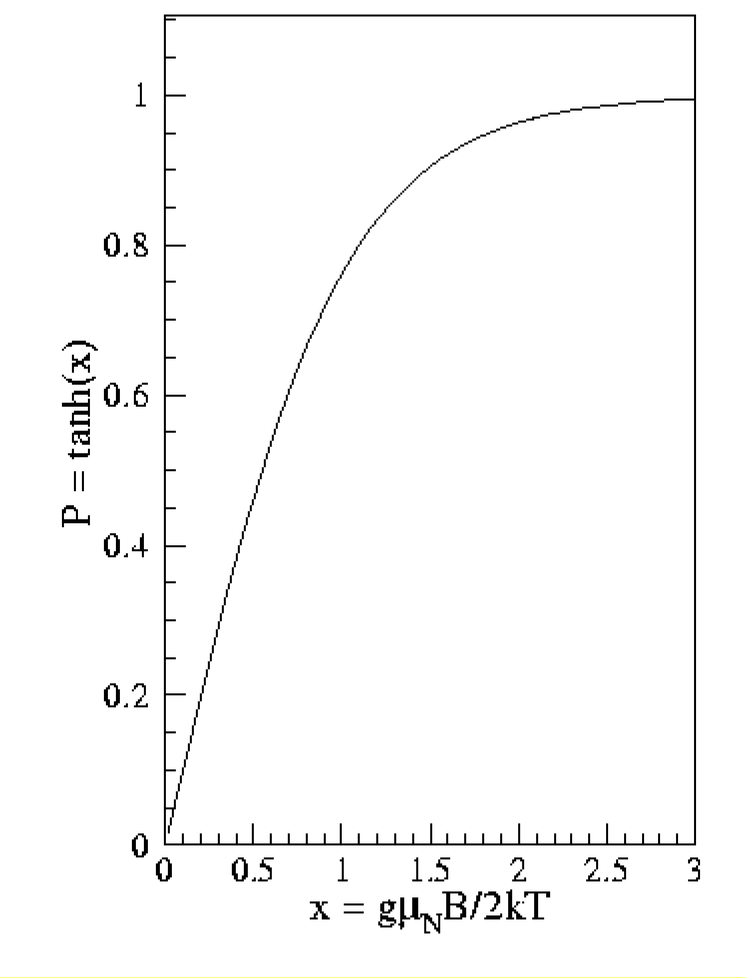
For I=1/2,



$$P = \frac{N_+ - N_-}{N_+ + N_-} = \frac{e^{\frac{\Delta E}{2kT}} - e^{\frac{-\Delta E}{2kT}}}{e^{\frac{\Delta E}{2kT}} + e^{\frac{-\Delta E}{2kT}}} = \tanh(x)$$

$\sim \underline{x \text{ (for x << 1)}}$

where $x = \frac{\Delta E}{2kT} = g_{He}\mu_N B/2kT$



³He : $x = g_{He}\mu_N B/2kT = 8.00{*}10^{-4}\, B(\mathrm{T})/T(\mathrm{K})$

Expected NMR signal is proportional to $N_+ - N_-$

	Protons in 1.5 T	
Polarization	$5.2 \cdot 10^{-6}$	
$N_+ - N_- =$	$3.5 \cdot 10^{14}$	in 1 μ*l* of water
$P \cdot (N_+ + N_-)$	$3.5 \cdot 10^{9}$	in 1 μ*l* of air (rel. humidity 60%)

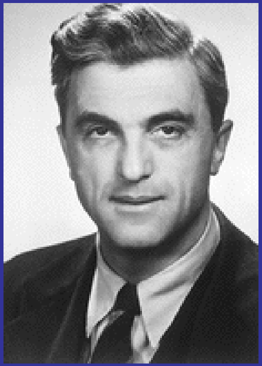
at room temperature, in thermal equilibrium

However, if P becomes 5.2×10^{-1}, then $(N^+ - N^-)$ becomes 3.5×10^{14} even in 1μl air irrespectively of B strength.

This is a basic principle of hyperpolarized NMR

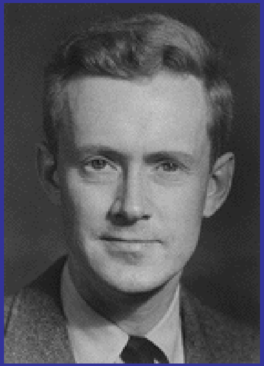
1.3. *Short history of NMR/MRI*

- **1933 Stern et al. discover the magnetic moment of proton.**
- **1938 Rabi discovers Nuclear Magnetic Resonance (NMR) on molecular beams.**
- **1946 F. Bloch and E. Purcell independently describe NMR on condensed matter.**

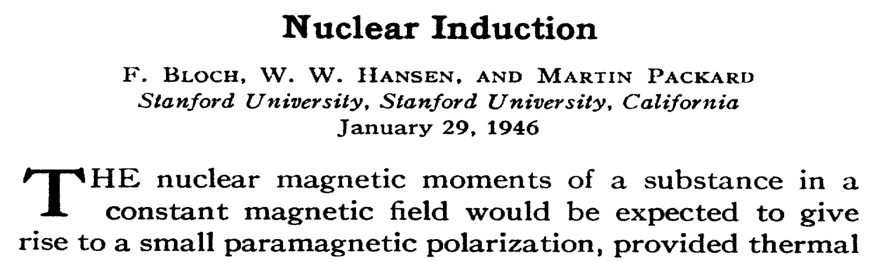


Felix Bloch

Same volume of Phys. Rev in 1946



Edward Purcell

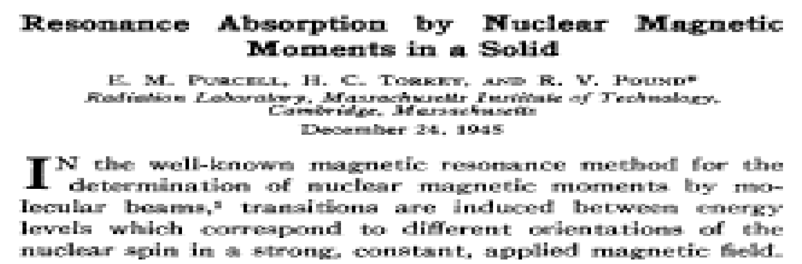


Nuclear Induction

F. Bloch, W. W. Hansen, and Martin Packard
Stanford University, Stanford University, California
January 29, 1946

THE nuclear magnetic moments of a substance in a constant magnetic field would be expected to give rise to a small paramagnetic polarization, provided thermal

proton NMR in water



Resonance Absorption by Nuclear Magnetic Moments in a Solid

E. M. Purcell, H. C. Torrey, and R. V. Pound*
Radiation Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts
December 24, 1945

IN the well-known magnetic resonance method for the determination of nuclear magnetic moments by molecular beams,[1] transitions are induced between energy levels which correspond to different orientations of the nuclear spin in a strong, constant, applied magnetic field.

Proton NMR in paraffin

- 1950 Proctor and Yu discover chemical shift due to molecular environment of protons. NMR becomes an essential tool of analytical chemistry.
- 1971 Damadian proposes how some cancerous tissues respond differently to magnetic fields than normal tissue, i.e., the difference of relaxation times
- 1973 P. C. Lauterbur realized that if a nonuniform magnetic field was used, then the radio signals would come from just one slice of the sample, allowing a two-dimensional image to be created.

1975 R. Ernst et al. establish the concept of Fourier transform imaging nowadays widely used.

- 1977 Sir P. Mansfield took a first image on a finger of human being.
- 1979 Moor et al. took the first images in multiple orientations of human brain

Paul C. Lauterbur **Sir Peter Mansfield**

Nobel Prize in Medicine 2003

P. C. Lauterbur's first imaging for proton in water

When he submitted his paper to Nature, the journal editor rejected publication. Then, he persuaded the editor to accept his paper.

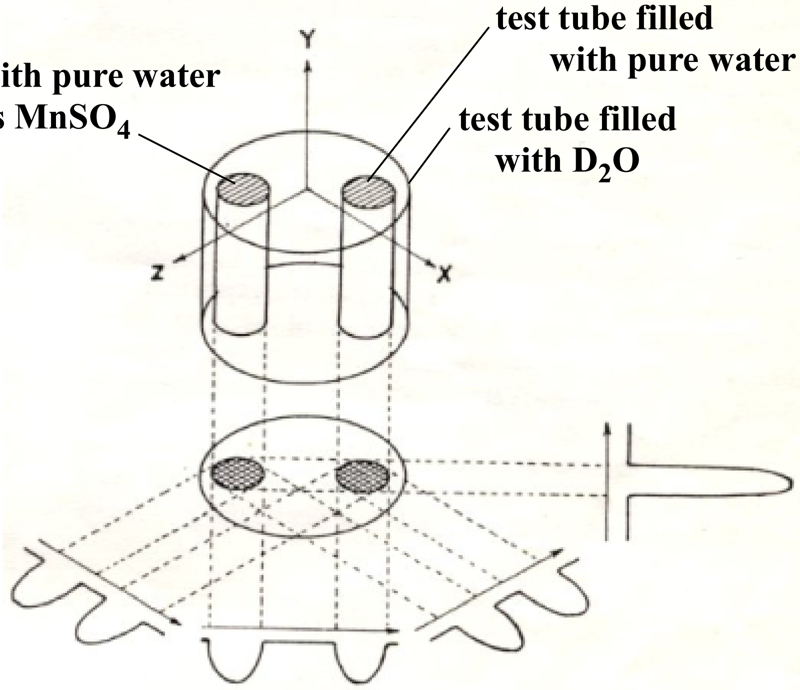


Fig. 1 Relationship between a three-dimensional object, its two-dimensional projection along the Y-axis, and four one-dimensional projections at 45° intervals in the XZ-plane. The arrows indicate the gradient directions.

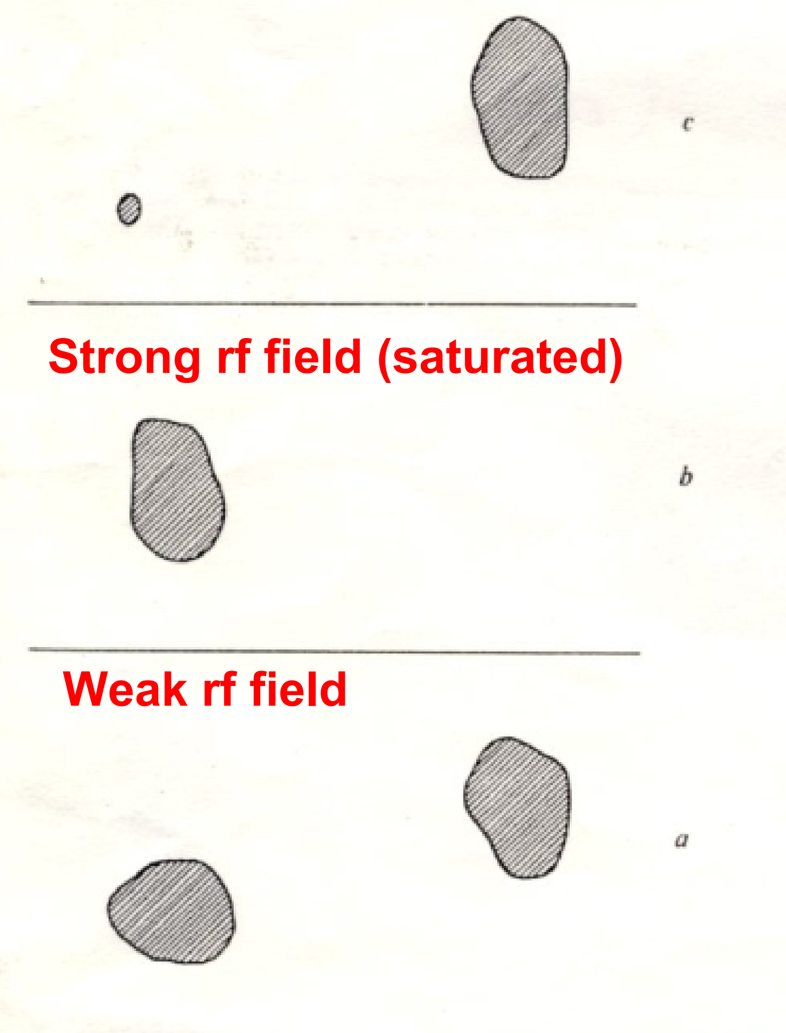
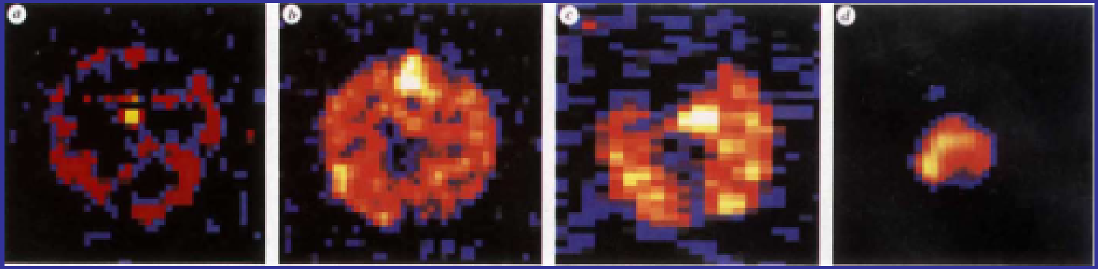


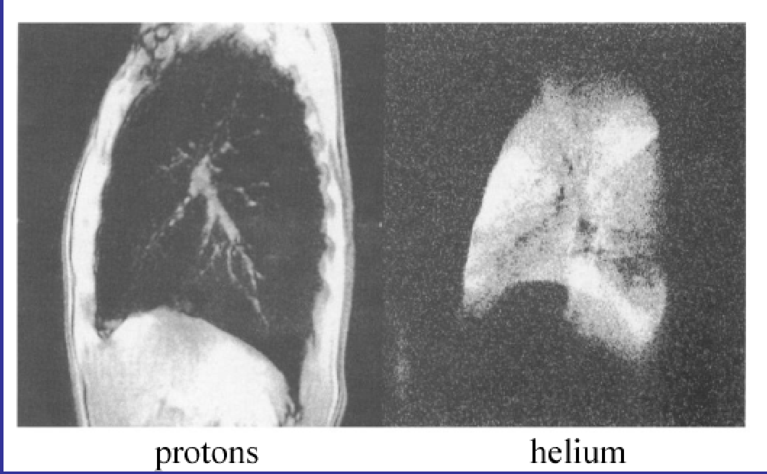
Fig. 3 Proton nuclear magnetic resonance zeugmatograms of an object containing regions with different relaxation times.

- 1994 M. Albert et al. succeed observation of a lung image of a mouse with a hyperpolarized ^{129}X gas (published in Nature).



- 1995 H. Middleton (Duke), and W. Happer (Princeton) took a lung MRI shot of a Guinea pig with a hyperpolarized ^{3}He gas. (Physics Today, June 1995).

- 1996 Otten, Heil et al. (Mainz) took the first human lung images at the Krebsforschung Zentrum, Heidelberg.



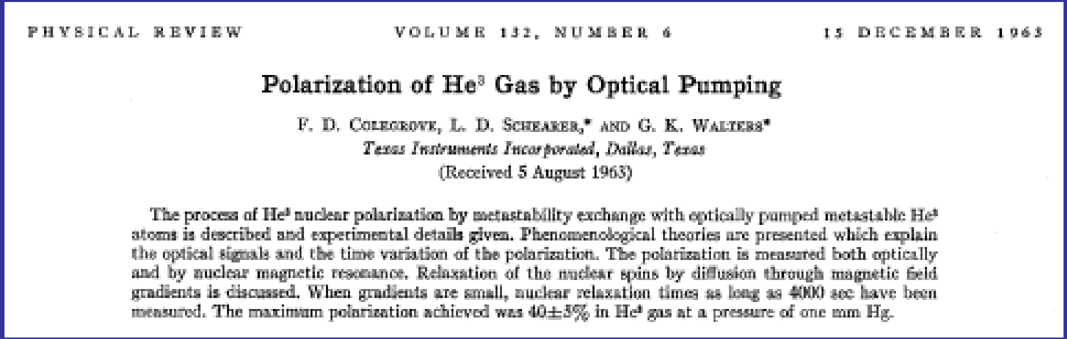
- # Production of polarized ^{3}He gas

A number of methods to polarize ^{3}He were proposed including the latest development of the DNP (Dynamic Nuclear Polarization) at Yamagata University.

However, the methods which enable to produce a large amount of highly polarized ^{3}He gas are rather limited, only MEOP (Metastability Exchange Optical Pumping) and SEOP (Spin Exchange Optical Pumping) are potentially used.

2.1. *MEOP (Metastability Exchange Optical Pumping)*

- ☐ In 1963, The “Metastability Exchange Optical Pumping” was discovered by Colegrove, Schearer, and Walters (Texas Instruments) and later applied to a polarized ^{3}He$^+$ ion source at Rice/Texas A &M.



PHYSICAL REVIEW VOLUME 132, NUMBER 6 15 DECEMBER 1963

Polarization of He^3 Gas by Optical Pumping

F. D. Colegrove, L. D. Schearer,* and G. K. Walters*
Texas Instruments Incorporated, Dallas, Texas
(Received 5 August 1963)

The process of He^3 nuclear polarization by metastability exchange with optically pumped metastable He^3 atoms is described and experimental details given. Phenomenological theories are presented which explain the optical signals and the time variation of the polarization. The polarization is measured both optically and by nuclear magnetic resonance. Relaxation of the nuclear spins by diffusion through magnetic field gradients is discussed. When gradients are small, nuclear relaxation times as long as 4000 sec have been measured. The maximum polarization achieved was 40±5% in He^3 gas at a pressure of one mm Hg.

Principe of MEOP

Colegrove, Schearer, Walters, PR 132, 251(1963)

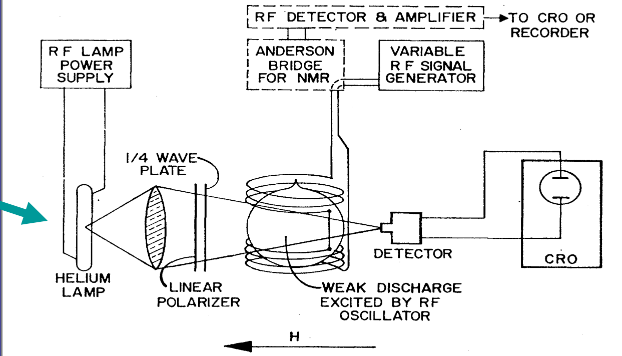
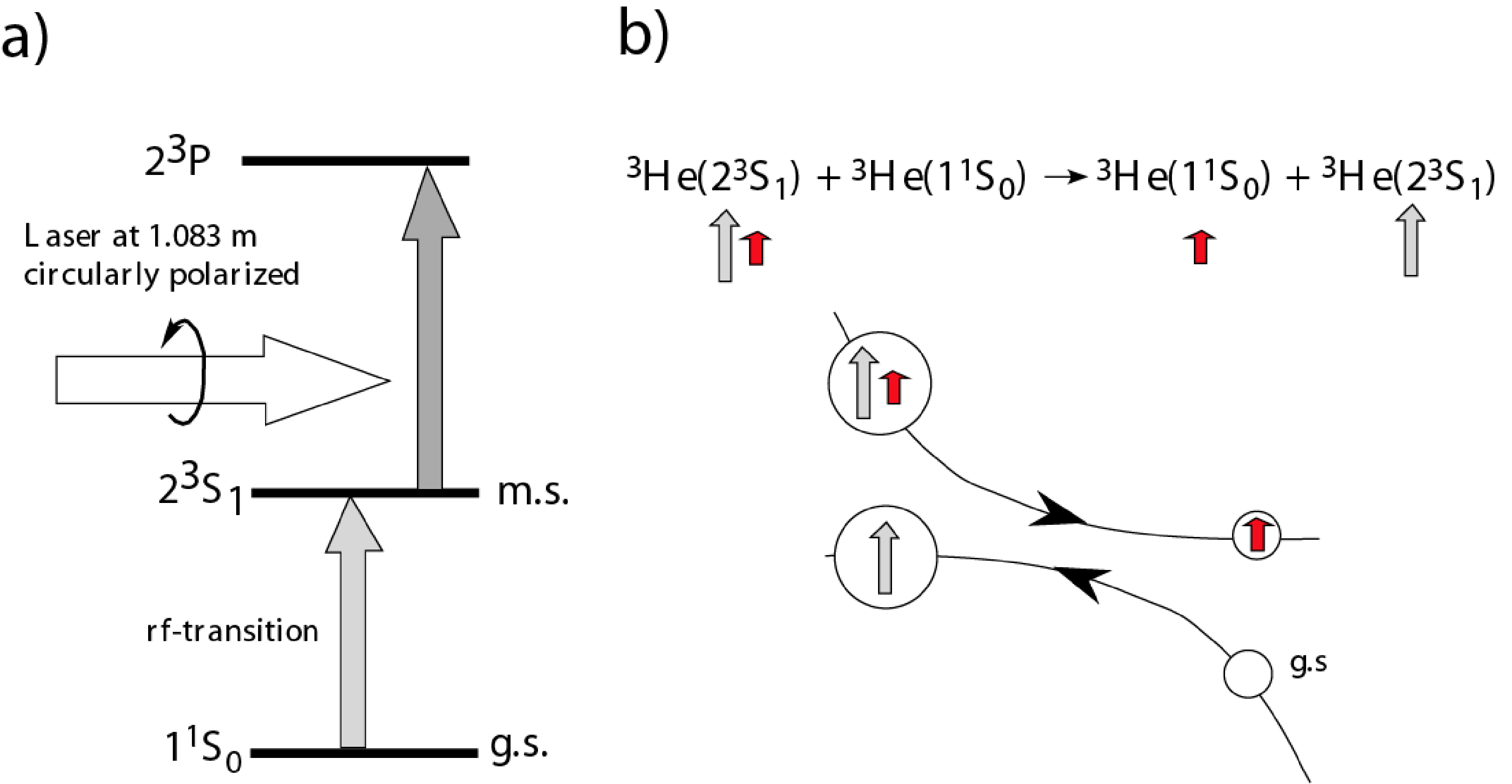


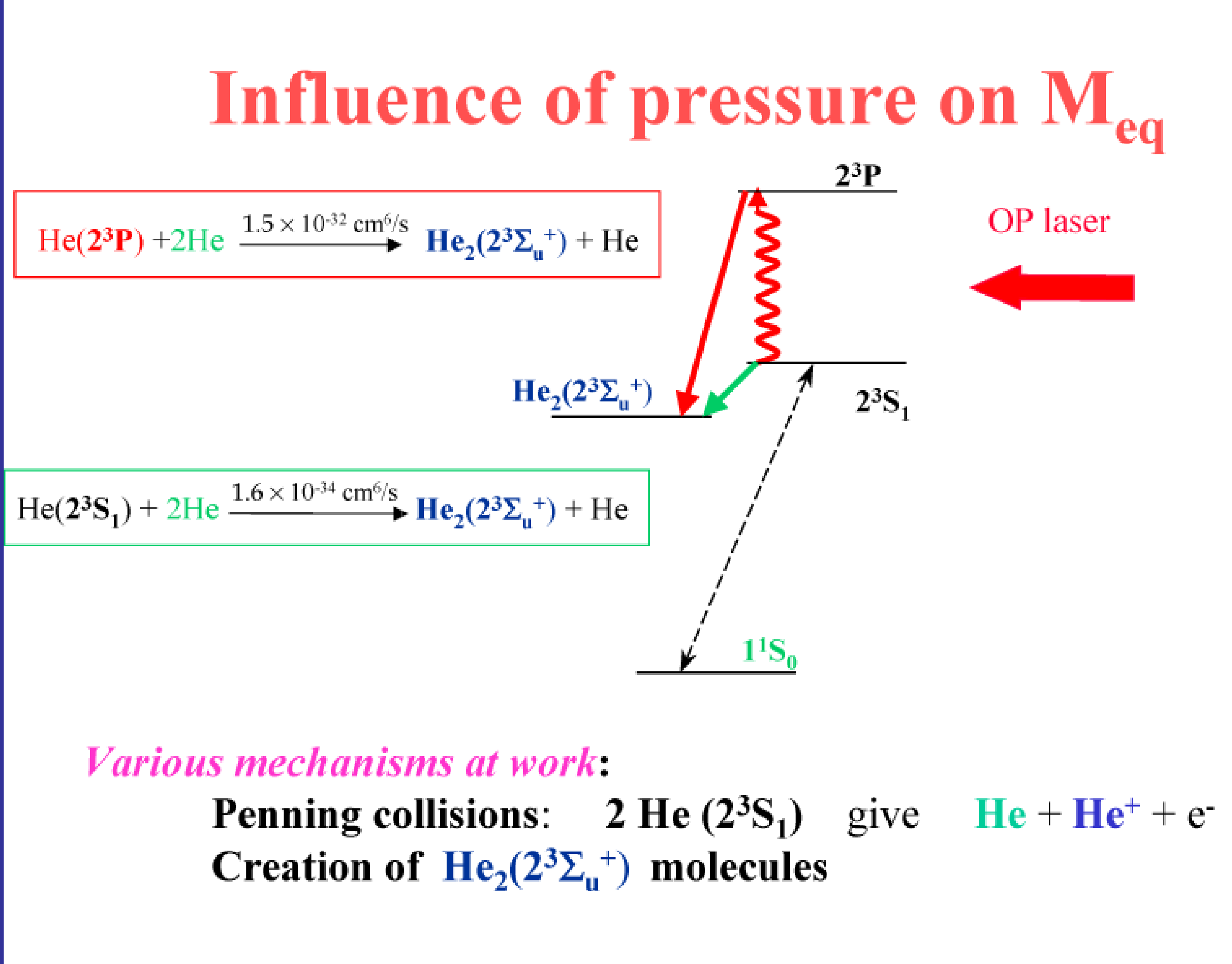
Fig. 6. Schematic of equipment used in performing resonance experiments on optically pumped He³.



Serious disadvantages of MEOP are

☐ Large ^{3}He polarization is obtained only at low gas pressures, whereas there is a serious depolarization during optical pumping at high gas pressure. To avoid this difficulty, OP is performed at low gas pressure.

Then, low pressure gas is compressed.



Influence of pressure on M_{eq}

$He(2^3P) + 2He \xrightarrow{1.5 \times 10^{-32}\ cm^6/s} He_2(2^3\Sigma_u^+) + He$

$He(2^3S_1) + 2He \xrightarrow{1.6 \times 10^{-34}\ cm^6/s} He_2(2^3\Sigma_u^+) + He$

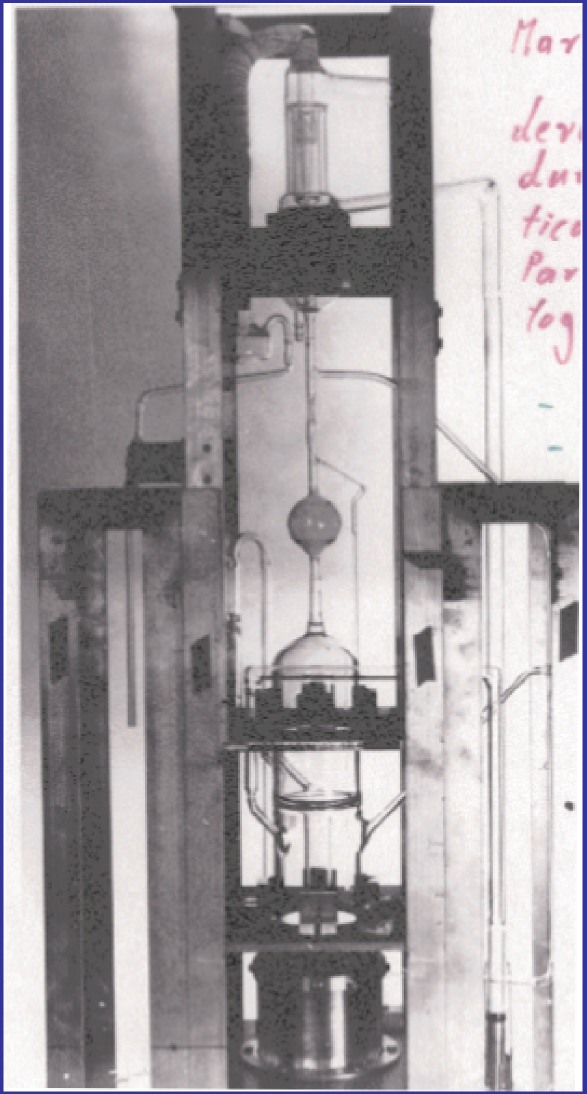
Various mechanisms at work:

Penning collisions: **2 He (2^3S_1)** give $He + He^+ + e^-$

Creation of $He_2(2^3\Sigma_u^+)$ molecules

^{3}He compressor

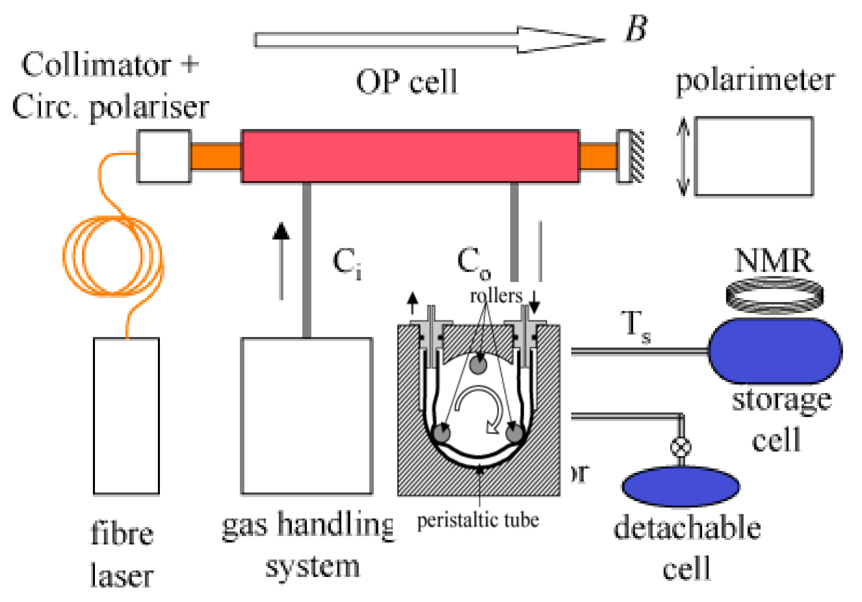
Otten in ENS/Paris



Toepler pump (1988-1993)

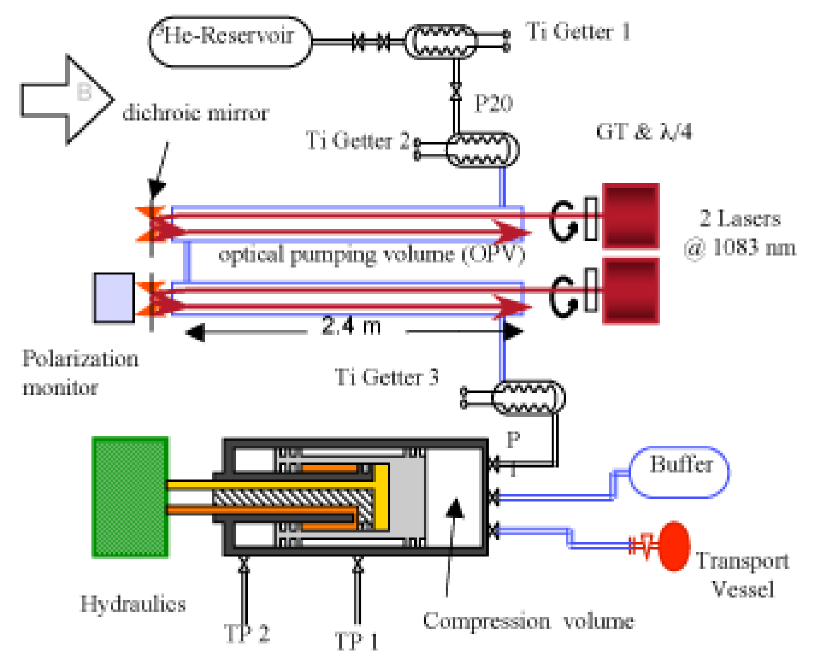
ENS

now



Mainz

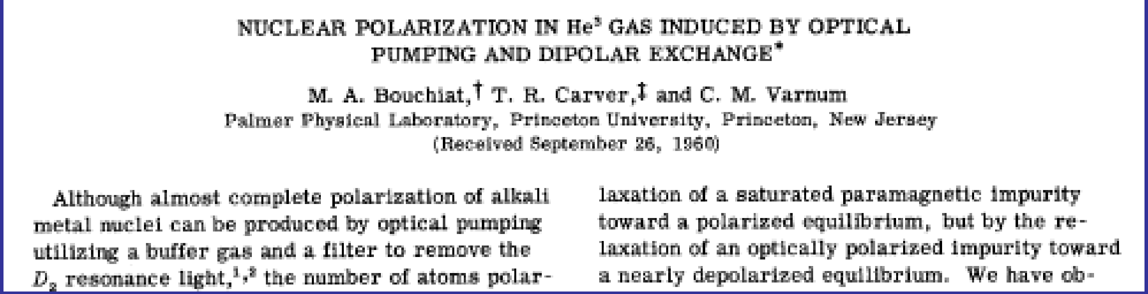
now



2.2. SEOP (Spin Exchange Optical Pumping)

A significant step to SEOP

- First ^{3}He-Rb spin-exchange



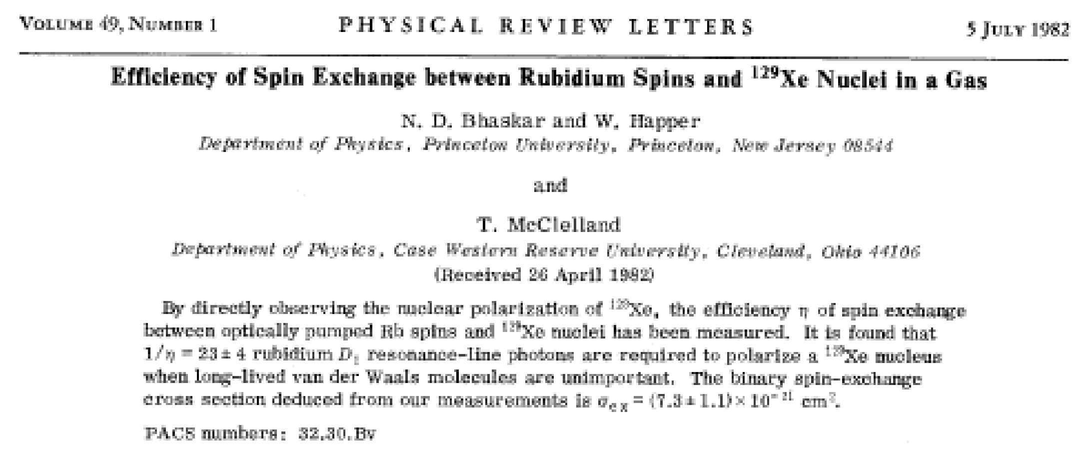
NUCLEAR POLARIZATION IN He^3 GAS INDUCED BY OPTICAL PUMPING AND DIPOLAR EXCHANGE*

M. A. Bouchiat,† T. R. Carver,‡ and C. M. Varnum
Palmer Physical Laboratory, Princeton University, Princeton, New Jersey
(Received September 26, 1960)

Although almost complete polarization of alkali metal nuclei can be produced by optical pumping utilizing a buffer gas and a filter to remove the D_2 resonance light,[1,2] the number of atoms polar-

laxation of a saturated paramagnetic impurity toward a polarized equilibrium, but by the relaxation of an optically polarized impurity toward a nearly depolarized equilibrium. We have ob-

1 First dense sample with high polarization (10%)



VOLUME 49, NUMBER 1 PHYSICAL REVIEW LETTERS 5 JULY 1982

Efficiency of Spin Exchange between Rubidium Spins and ^{129}Xe Nuclei in a Gas

N. D. Bhaskar and W. Happer
Department of Physics, Princeton University, Princeton, New Jersey 08544

and

T. McClelland
Department of Physics, Case Western Reserve University, Cleveland, Ohio 44106

(Received 26 April 1982)

By directly observing the nuclear polarization of ^{129}Xe, the efficiency η of spin exchange between optically pumped Rb spins and ^{129}Xe nuclei has been measured. It is found that $1/\eta = 23 \pm 4$ rubidium D_1 resonance-line photons are required to polarize a ^{129}Xe nucleus when long-lived van der Waals molecules are unimportant. The binary spin-exchange cross section deduced from our measurements is $\sigma_{ex} = (7.3 \pm 1.1) \times 10^{-21}$ cm^2.

PACS numbers: 32.30.Bv

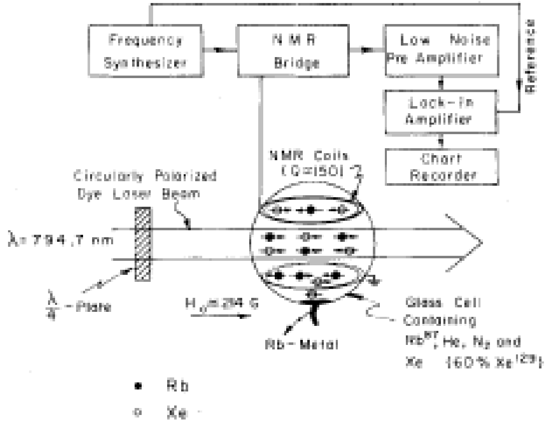
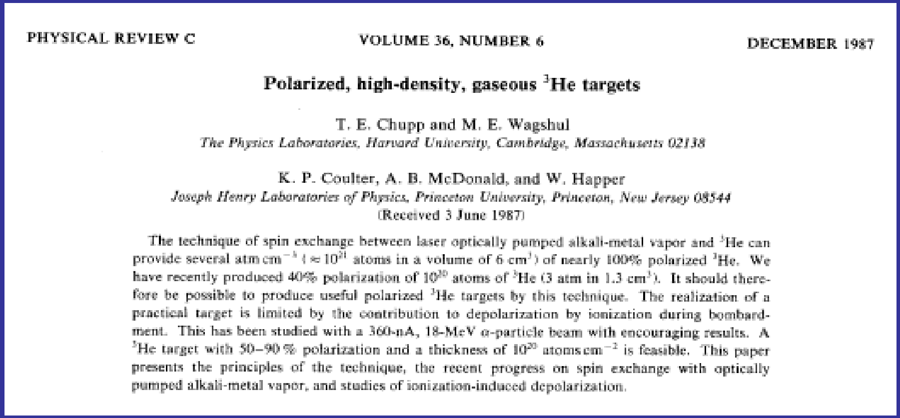


FIG. 1. NMR apparatus for measuring the absolute nuclear polarization in ^{129}Xe.

1987 First targets



PHYSICAL REVIEW C VOLUME 36, NUMBER 6 DECEMBER 1987

Polarized, high-density, gaseous ^{3}He targets

T. E. Chupp and M. E. Wagshul
The Physics Laboratories, Harvard University, Cambridge, Massachusetts 02138

K. P. Coulter, A. B. McDonald, and W. Happer
Joseph Henry Laboratories of Physics, Princeton University, Princeton, New Jersey 08544

(Received 3 June 1987)

The technique of spin exchange between laser optically pumped alkali-metal vapor and ^{3}He can provide several atm cm^{-3} ($\approx 10^{21}$ atoms in a volume of 6 cm^3) of nearly 100% polarized ^{3}He. We have recently produced 40% polarization of 10^{20} atoms of ^{3}He (3 atm in 1.3 cm^3). It should therefore be possible to produce useful polarized ^{3}He targets by this technique. The realization of a practical target is limited by the contribution to depolarization by ionization during bombardment. This has been studied with a 360-nA, 18-MeV α-particle beam with encouraging results. A ^{3}He target with 50–90 % polarization and a thickness of 10^{20} atoms cm^{-2} is feasible. This paper presents the principles of the technique, the recent progress on spin exchange with optically pumped alkali-metal vapor, and studies of ionization-induced depolarization.

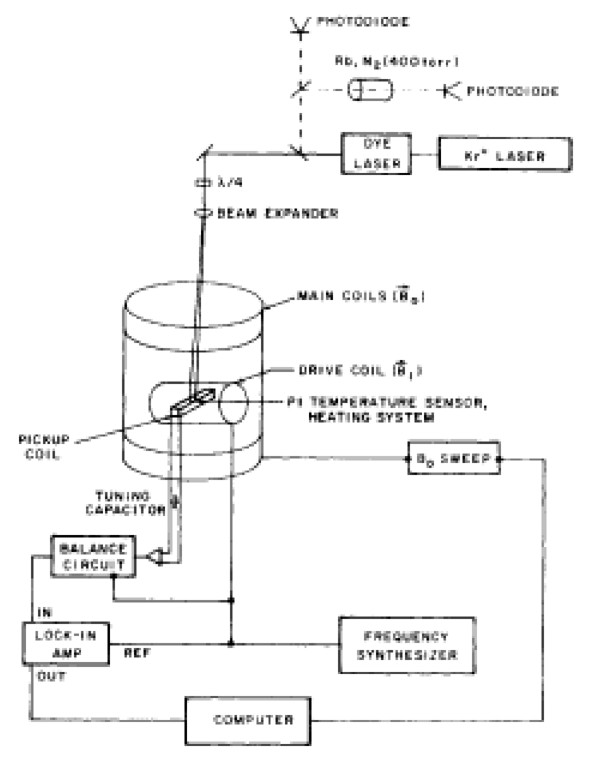
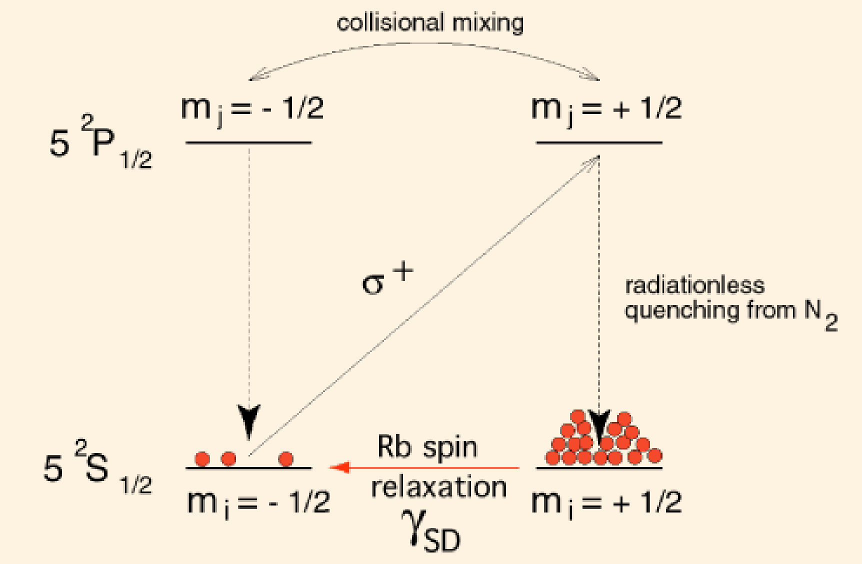
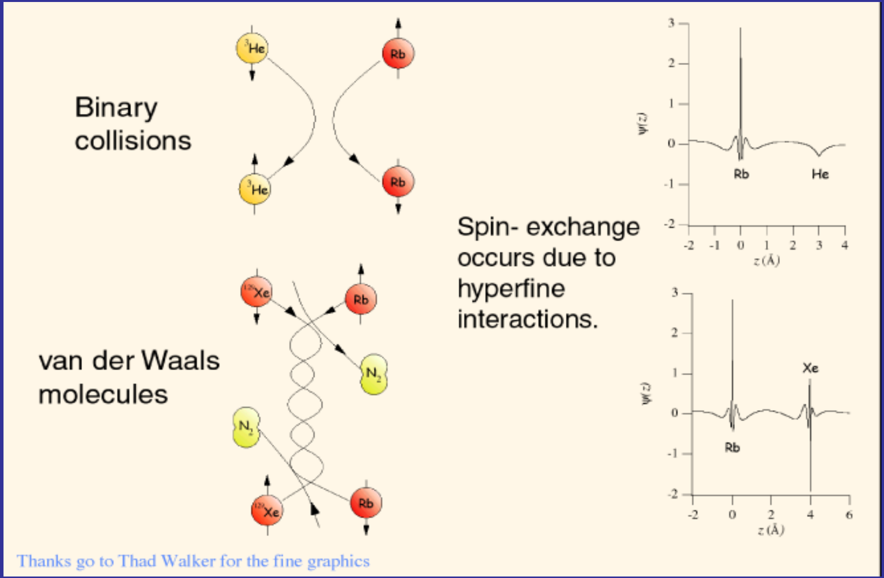


FIG. 2. NMR-AFP polarimeter. B_0 corresponds to B_z and B_1 to B_x.

Polarization of Rb atom



Polarization of ^{3}He atom



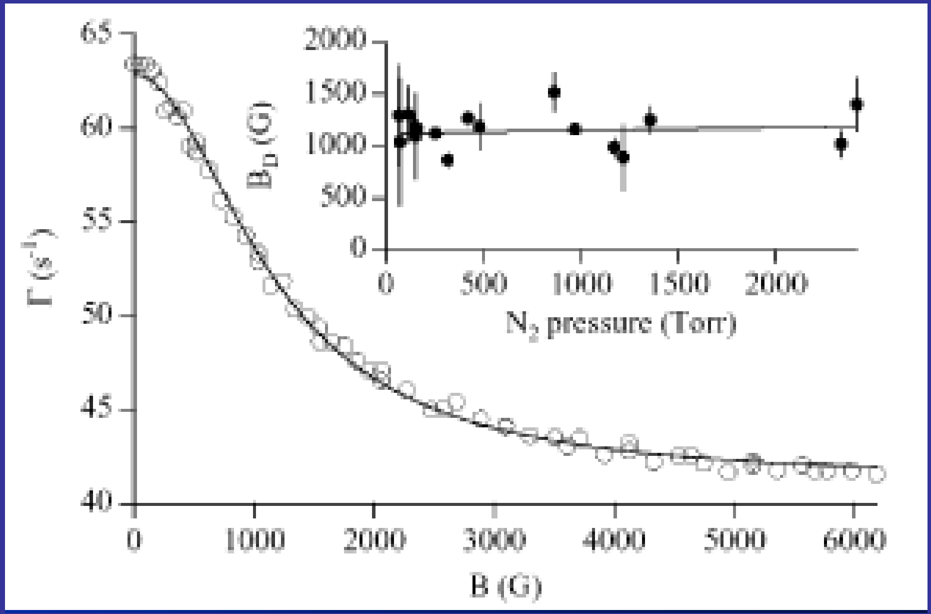
Spin- exchange occurs due to hyperfine interactions.

Thanks go to Thad Walker for the fine graphics

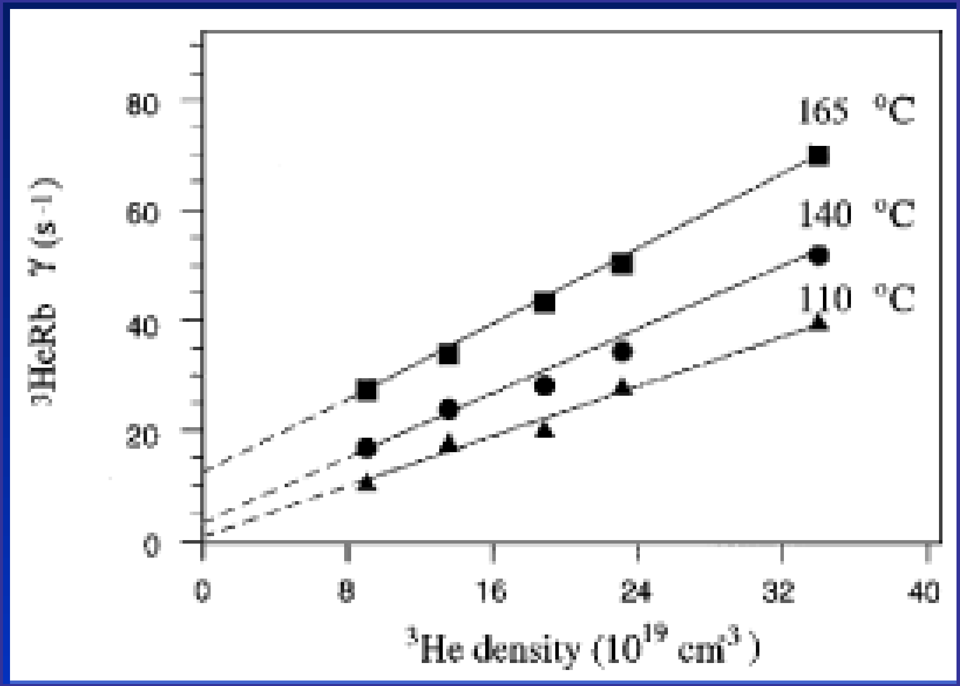
The origin of ^{3}He nuclear spin relaxation

- ☐ ^{3}He-^{3}He dipolar relaxation in the bulk
- ☐ Wall relaxation
  - Ferromagneitc sites
  - Other unwanted surface contamination
- ☐ Magnetic field inhomogeneities
- ☐ Other relaxations
- ☐ Hysterisis relaxation:
  - large change in wall relaxation due solely to previous exposure to a large magnetic field

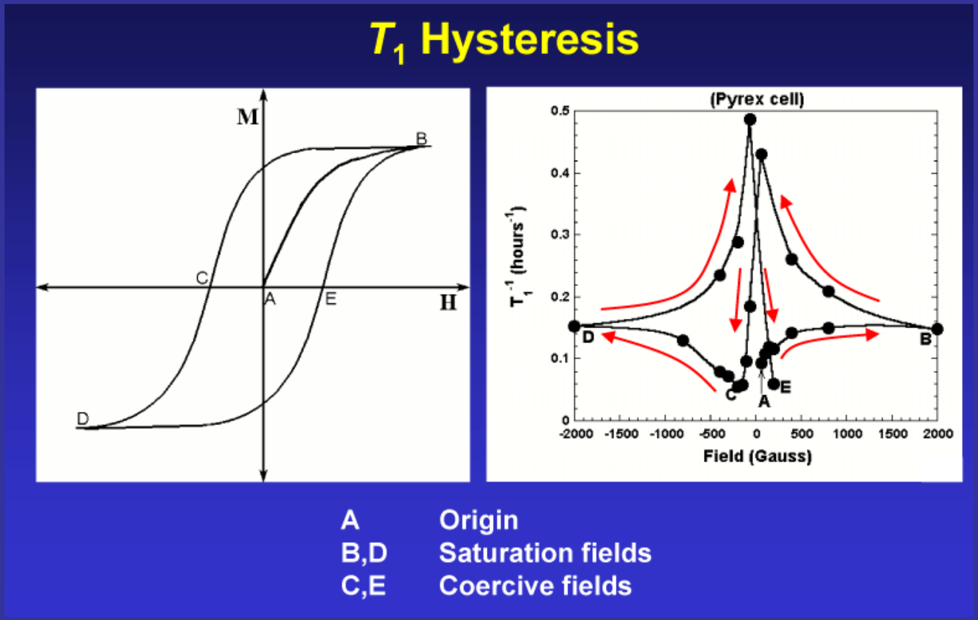
1 **Kadlecek et al. discovered a strong magnetic field dependence in the Rb relaxation which is due to the formation of triplet Rb_2 dimers as an important sources of relaxation**



1 **Baranga et al. showed that relaxation due to Rb - ^{3}He collisions often accounts for a least half the relaxation.**

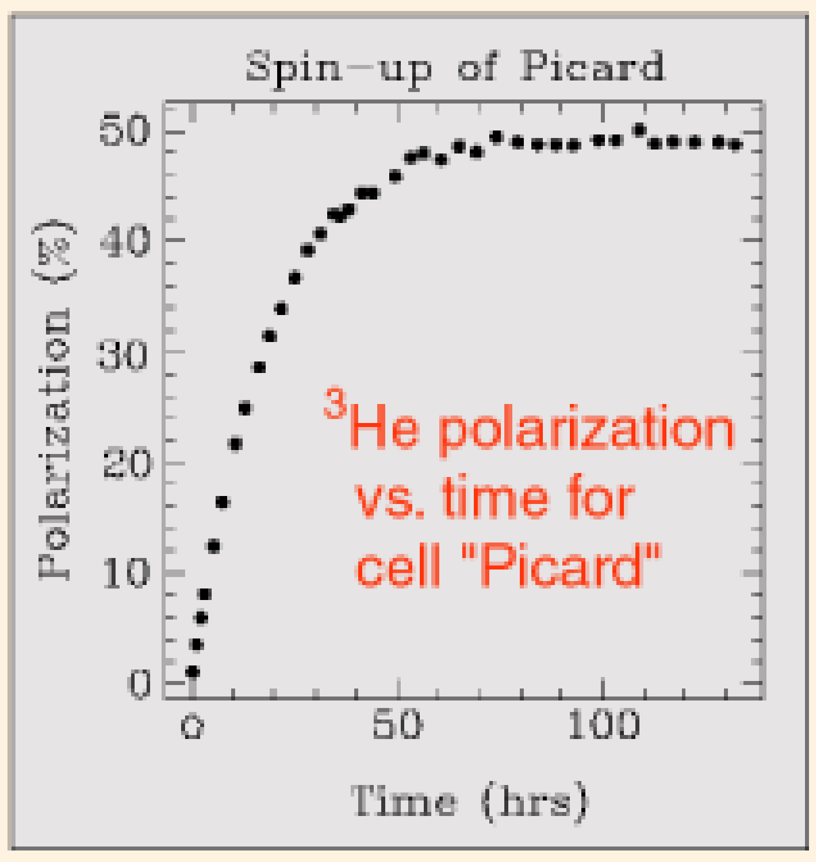


- The T_1 hysterisis and correlation with presence of Rb atom was discovered by the group from Utah



T_1 Hysteresis

A	Origin
B,D	Saturation fields
C,E	Coercive fields

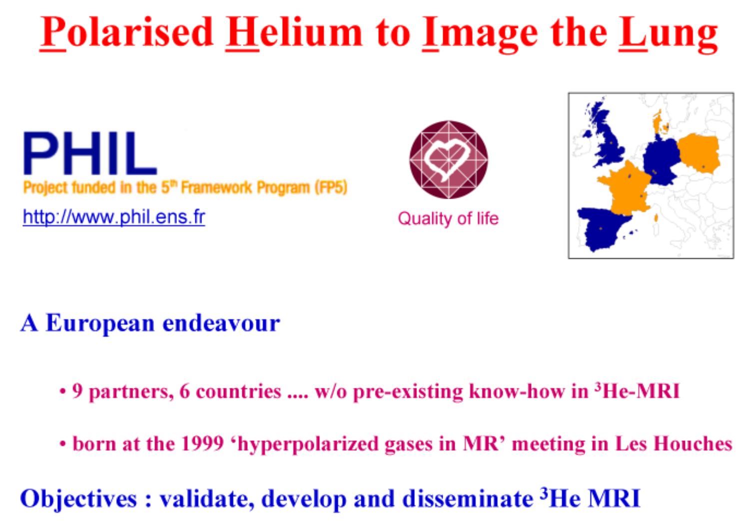


^{3}He polarization vs. time for cell "Picard"

Importance of surface treatment of cell!

• Application to the medical research

3.1. Network



Polarised Helium to Image the Lung

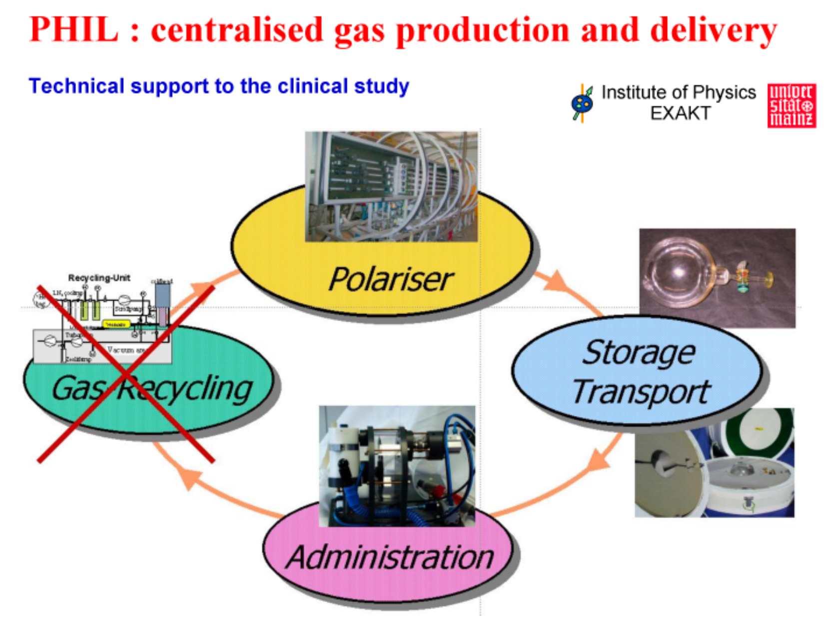
PHIL
Project funded in the 5th Framework Program (FP5)
http://www.phil.ens.fr

Quality of life

A European endeavour

- 9 partners, 6 countries .... w/o pre-existing know-how in ^{3}He-MRI
- born at the 1999 ‘hyperpolarized gases in MR’ meeting in Les Houches

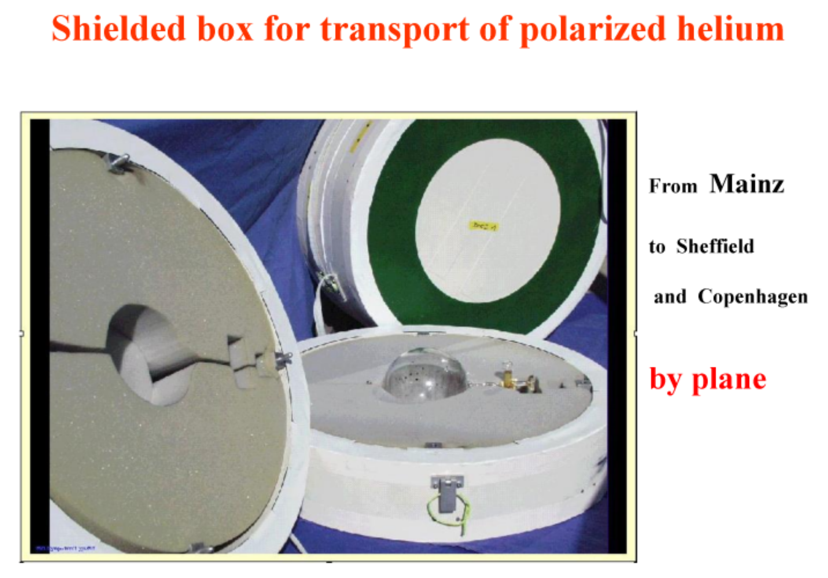
Objectives : validate, develop and disseminate ^{3}He MRI



PHIL : centralised gas production and delivery

Technical support to the clinical study

Institute of Physics
EXAKT



Shielded box for transport of polarized helium

From **Mainz**

to **Sheffield**

and **Copenhagen**

by plane

Now called

PHELINET

Polarized Helium Lung

Imaging Network

Innovative, non-invasive lung MRI techniques for clinical diagnosis and validation of lung therapy. Research and Training Network (RTN) – Marie Curie Action – 6th Framework Program (2007-2010)

3.2. Present research on lung imaging

Measurable quantities of polarized ^{3}He are

1) **static distribution**
2) **gas diffusion - ADC**
3) **nuclear spin relaxation - pO_2**

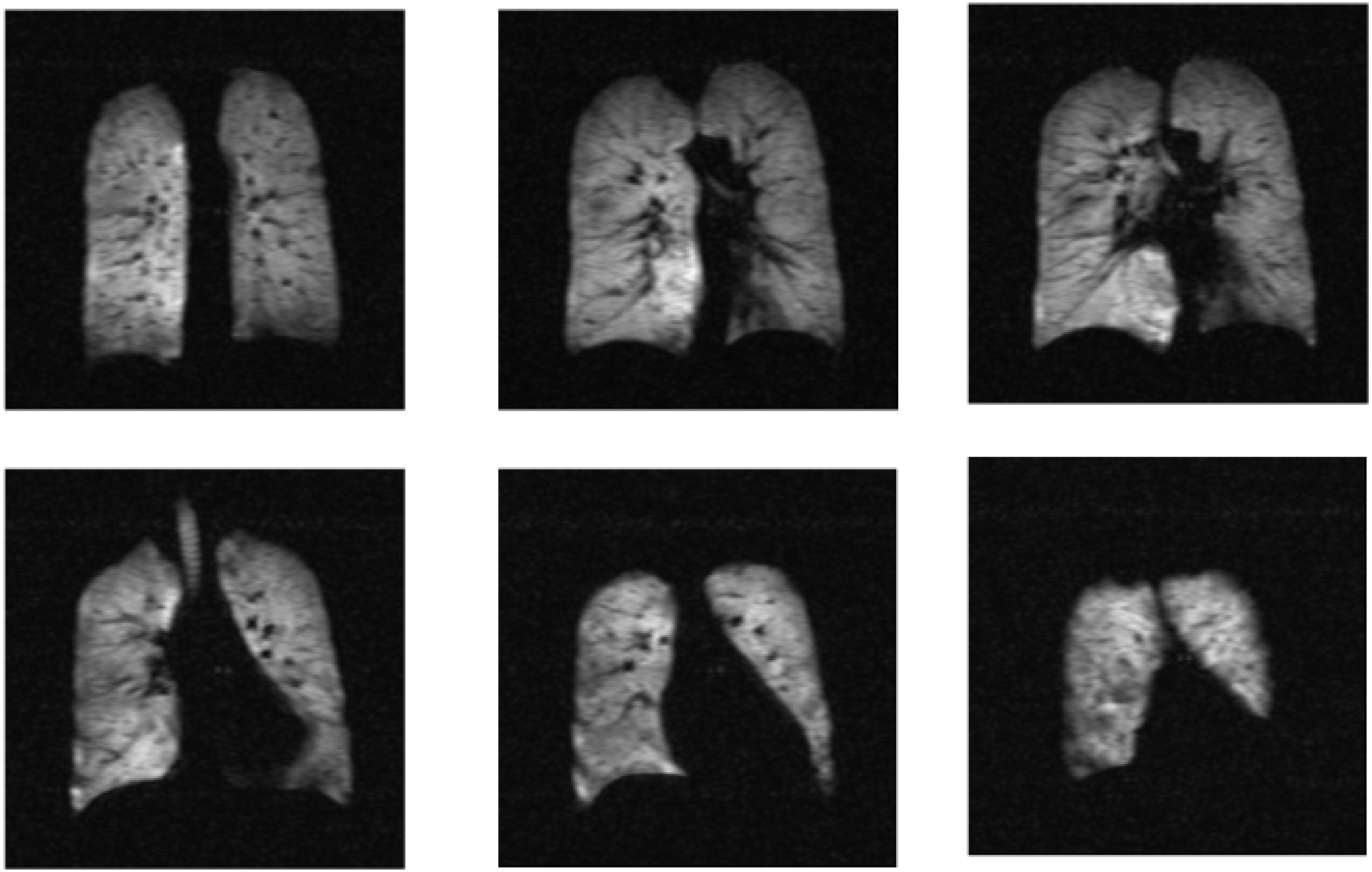
Most of them are ready for use in clinical application, such as diagnosis of COPD (Chronical Obstructive Pulmonary Disease) on the basis of a plenty amount of data accumulation so far.

To comprehensively talk about them is, of course, beyond my scope. Therefore, I will confine my talk only on some of them from my personal interest.

3.2.I. Static distribution

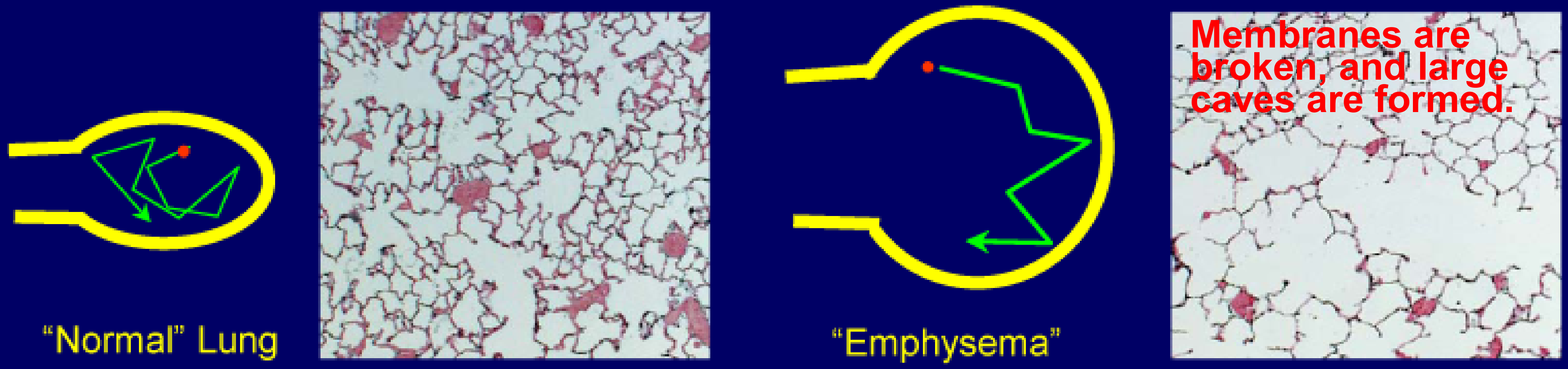
Obtained by Holding a respiration

Anatomic cuts (1cm thick)



3.2.2. Diffusion

Structure of Aeveolar, which is an end tissue of lung

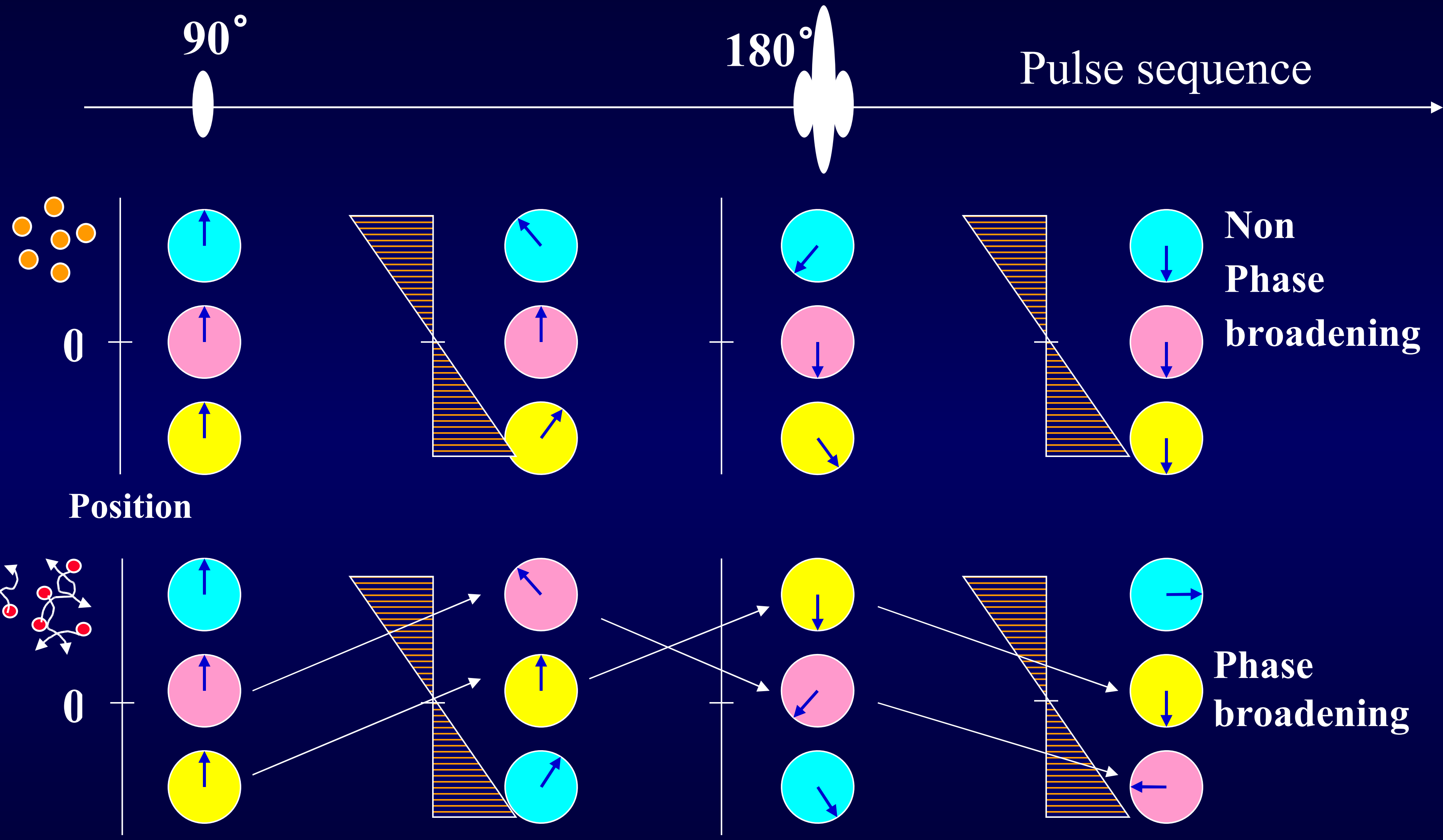


Principle to measure the diffusion coefficient:

The concept of ADC (Apparent Diffusion Coefficient) is frequently used. The ADC is defined as a diffusion coefficient ignoring the temperature difference and density difference.

The method uses a pulse sequence of 90°pulse followed by 180°pulse under the magnetic field with field gradient as shown in the next slide.

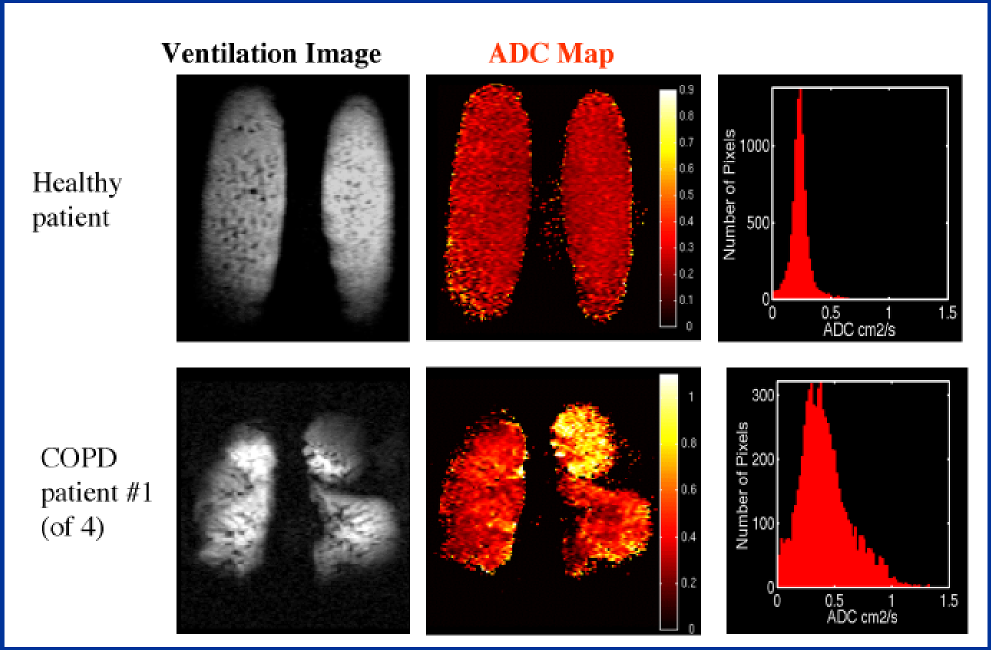
Phase broadening due to diffusion

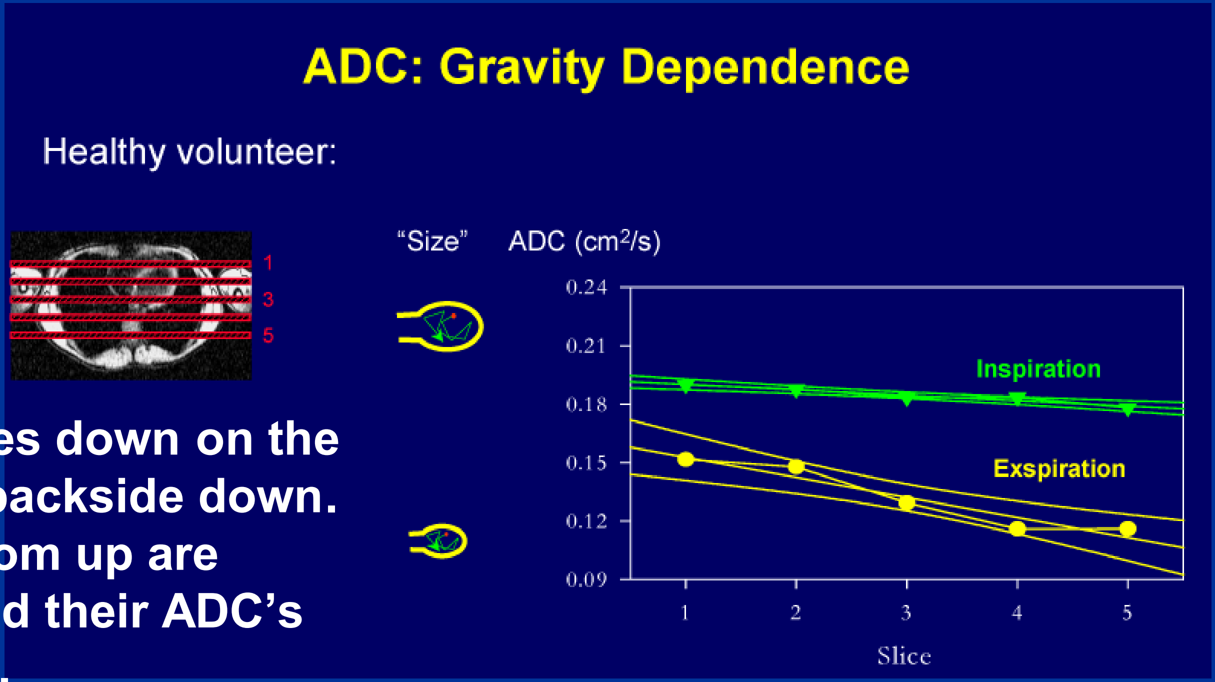


Non Phase broadening

Phase broadening

Displacement causes phase broadening





ADC: Gravity Dependence

Healthy volunteer:

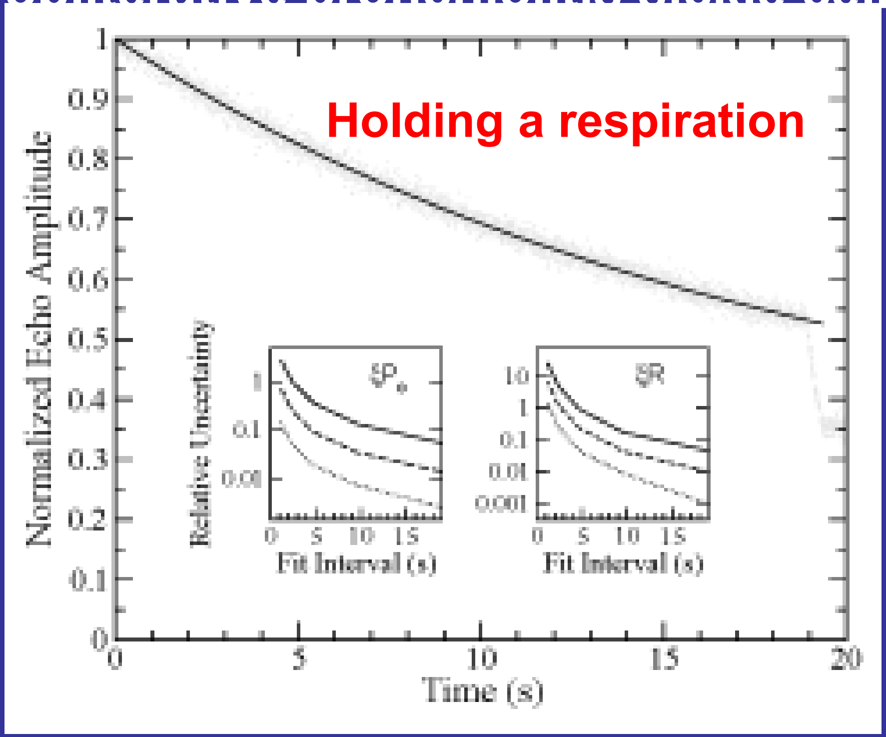
A volunteer lies down on the bed with his backside down. Five slices from up are numbered, and their ADC's are measured.

3.2.3. pO_2 (partial pressure of O_2)

The partial pressure of oxygen (pO_2) and its depletion rate are important parameters in lung function assessment. Aeveolar pO_2 can be used as a marker of ventilation efficiency, and the oxygen depletion rate, which is related to oxygen uptake, can be used to characterize perfusion. It has been shown that measuring the time evolution of pO_2 enables differentiation between normal and diseased lungs in pulmonary embolism, obliterative bronchiolitis sickle cell disease, and COPD.

Use of relaxation time in the Presence of Oxygen

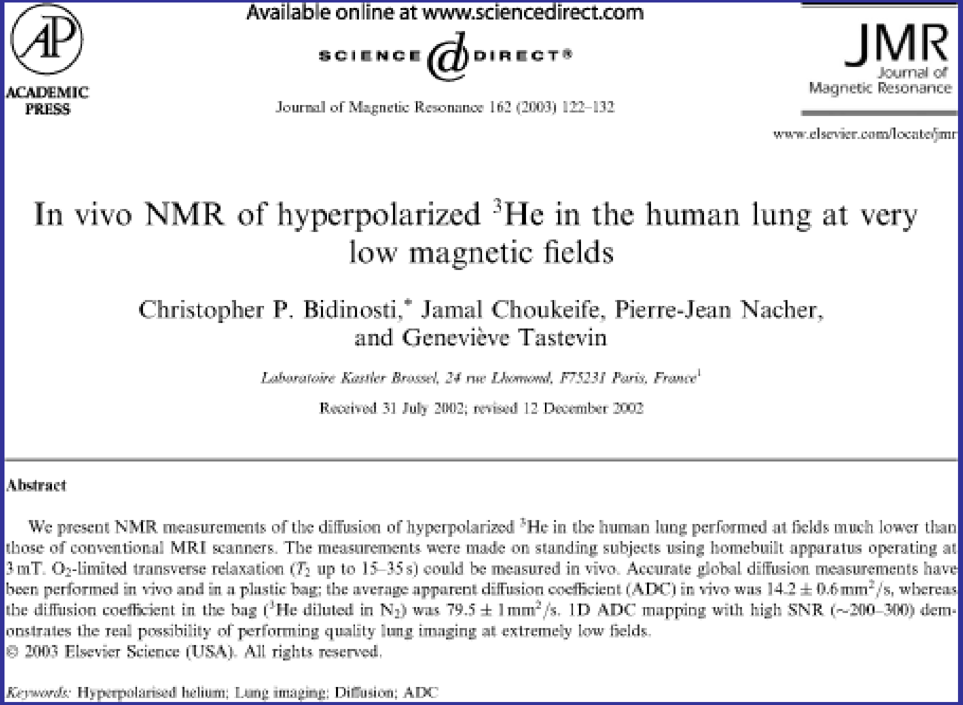
T_1 ~ 10-20 sec.


Holding a respiration

1. Future prospect

4.1. ^{3}He – MRI at very low field – for convenience (ENS/Paris at first, later, Kracow/Poland, etc.)

Most MRI S/N is proportional to B, while ^{3}He-MRI is independent of B. Therefore, there is no benefit for ^{3}He-MRI at high B.



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In vivo NMR of hyperpolarized ^{3}He in the human lung at very low magnetic fields

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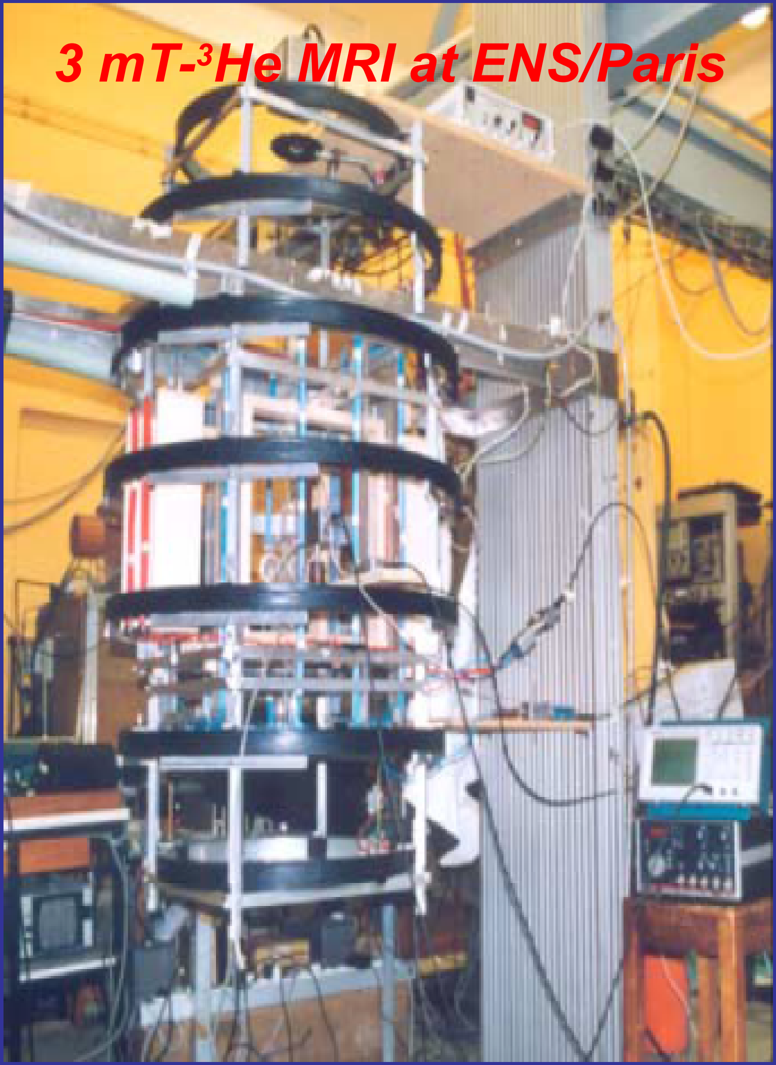
Abstract

We present NMR measurements of the diffusion of hyperpolarized ^{3}He in the human lung performed at fields much lower than those of conventional MRI scanners. The measurements were made on standing subjects using homebuilt apparatus operating at 3 mT. O_2-limited transverse relaxation (T_2 up to 15–35 s) could be measured in vivo. Accurate global diffusion measurements have been performed in vivo and in a plastic bag; the average apparent diffusion coefficient (ADC) in vivo was $14.2 \pm 0.6\,\mathrm{mm}^2/\mathrm{s}$, whereas the diffusion coefficient in the bag (^{3}He diluted in N_2) was $79.5 \pm 1\,\mathrm{mm}^2/\mathrm{s}$. 1D ADC mapping with high SNR (~200–300) demonstrates the real possibility of performing quality lung imaging at extremely low fields.

Keywords: Hyperpolarised helium; Lung imaging; Diffusion; ADC



3 mT-^{3}He MRI at ENS/Paris

Low field ^{3}He-MRI is advantageous from the following view points:

a) Local field gradients, which are due to spatial variations in tissue susceptibility, decrease in going to a lower imaging field.

b) Working at a reduced frequency reduces the RF power absorbed by the body, thereby allowing the use of rapid pulse sequences without exceeding safety limits.

c) Cost is greaty reduced. No need for superconducting magnet

Very important for future MRI

4.2. Project at RCNP/Osaka

- For high production

A brute force method:

Low Temperature and high magnetic filed

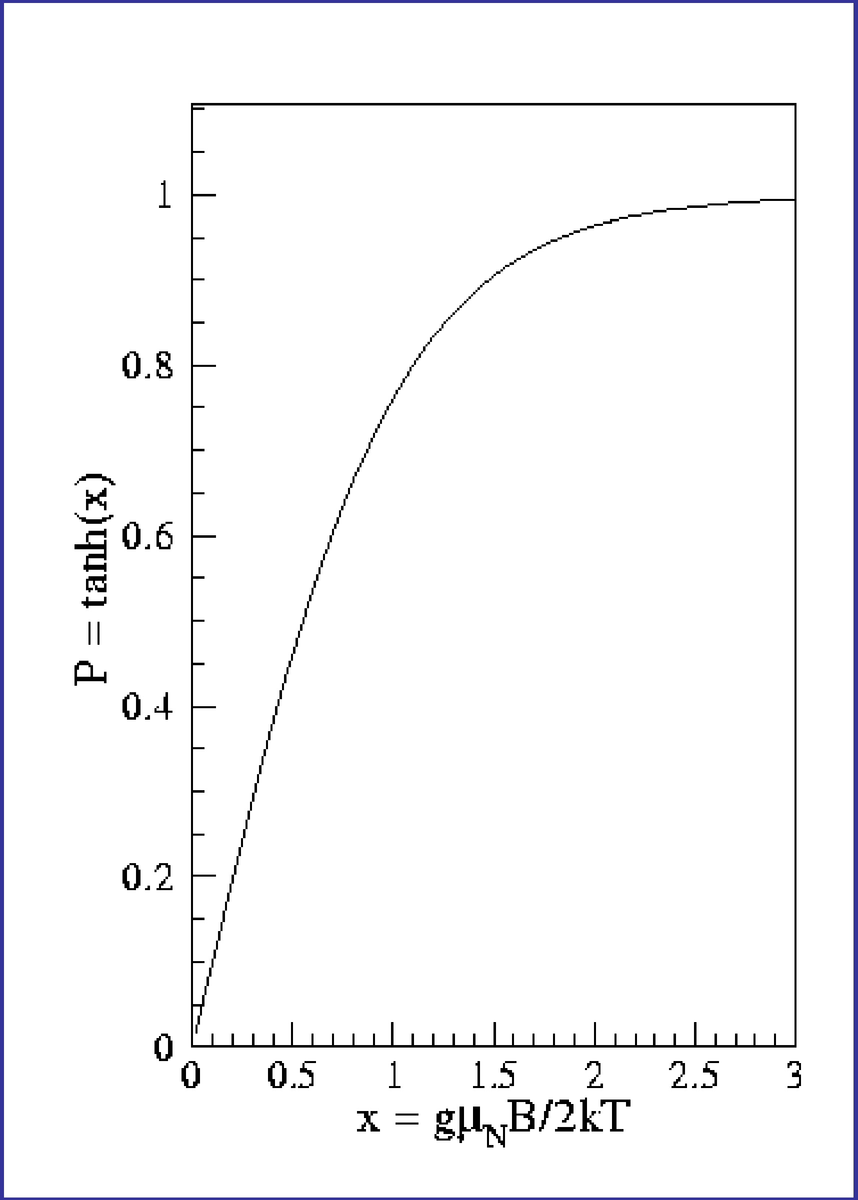
P = 95%

B = 15 T, T = 1 mK

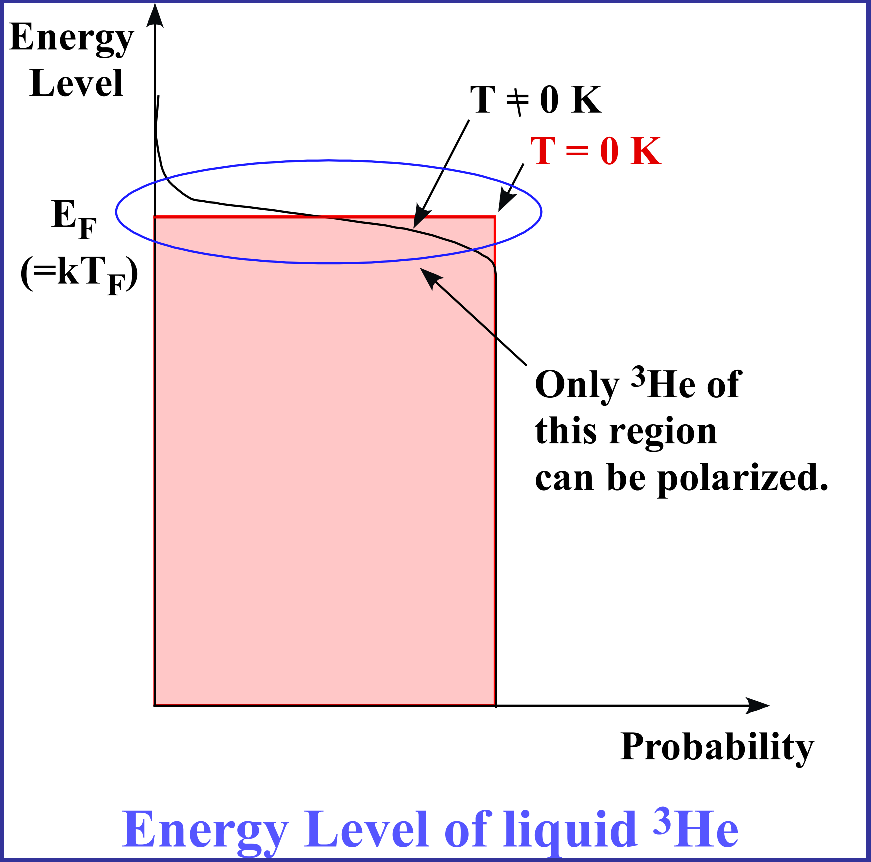
Is this true for ^{3}He ?

This is not true as far as liquid ^{3}He is concerned.

^{3}He polarization never obeys this graph, because ^{3}He is a Fermi particle.



Only a minor part of ^{3}He near the Fermi Energy can be polarized even if the temperature is lowered than 1 mK. In other words, the polarization can never be increased beyond the value at the Fermi temperature (T_F = 180 mK).



Energy Level of liquid ^{3}He

On the other hand, the solid ^{3}He does not obey this rule because the overlapping of wave function for ^{3}He is limited due to the long lattice separation.

In consequence, ^{3}He behaves as a paramagnetic substance for which the graph shown in the previous slide is valid.

The procedure to obtain highly polarized ^{3}He gas at room temperature – Idea of G. Frossati

- Formation of a solid ^{3}He cooled down to 1 mK by means of the Pomeranchuk cooling
- Polarization by means of the brute force method, i.e. B = 17 T and T = 1mK

expected solid polarization > 95%

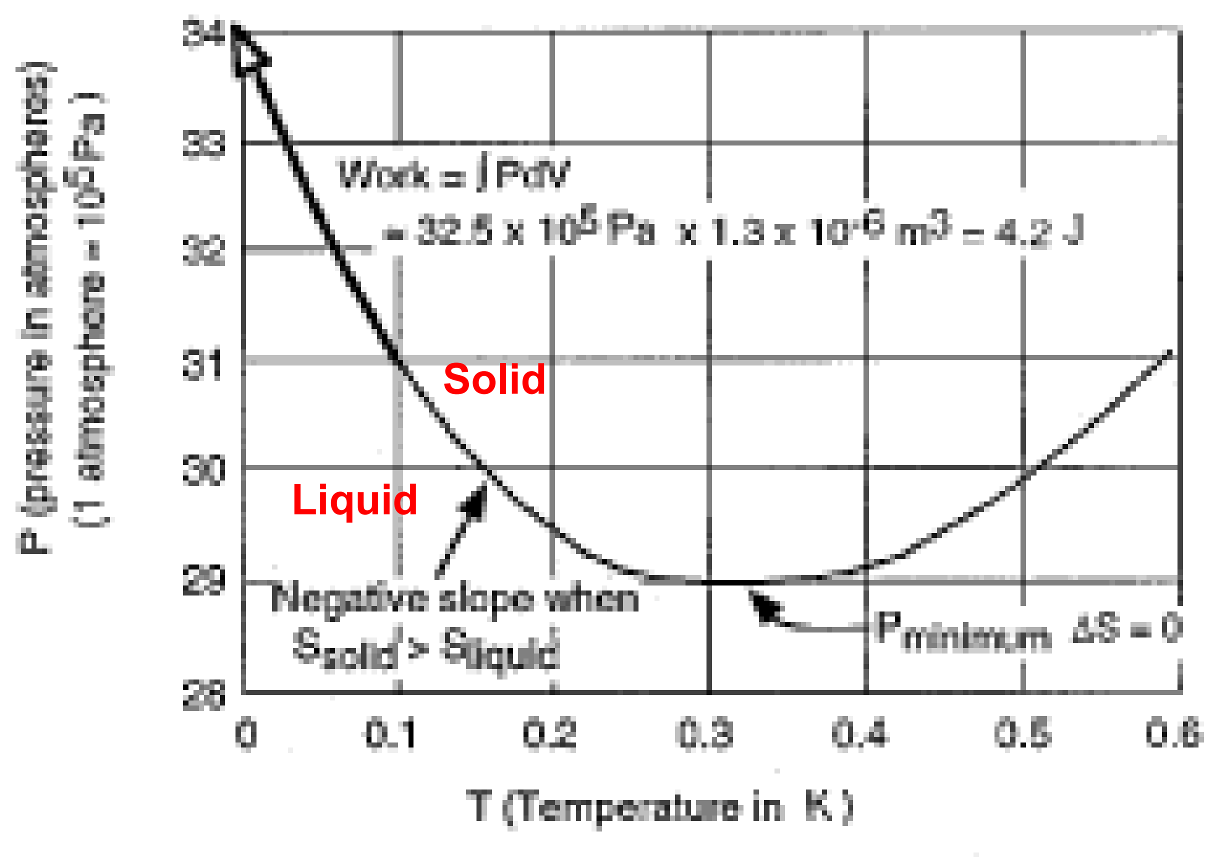
3) Rapid melting by decompression and gasification in a time shorter than the relaxation time.

Principle of Pomeranchuk cooling

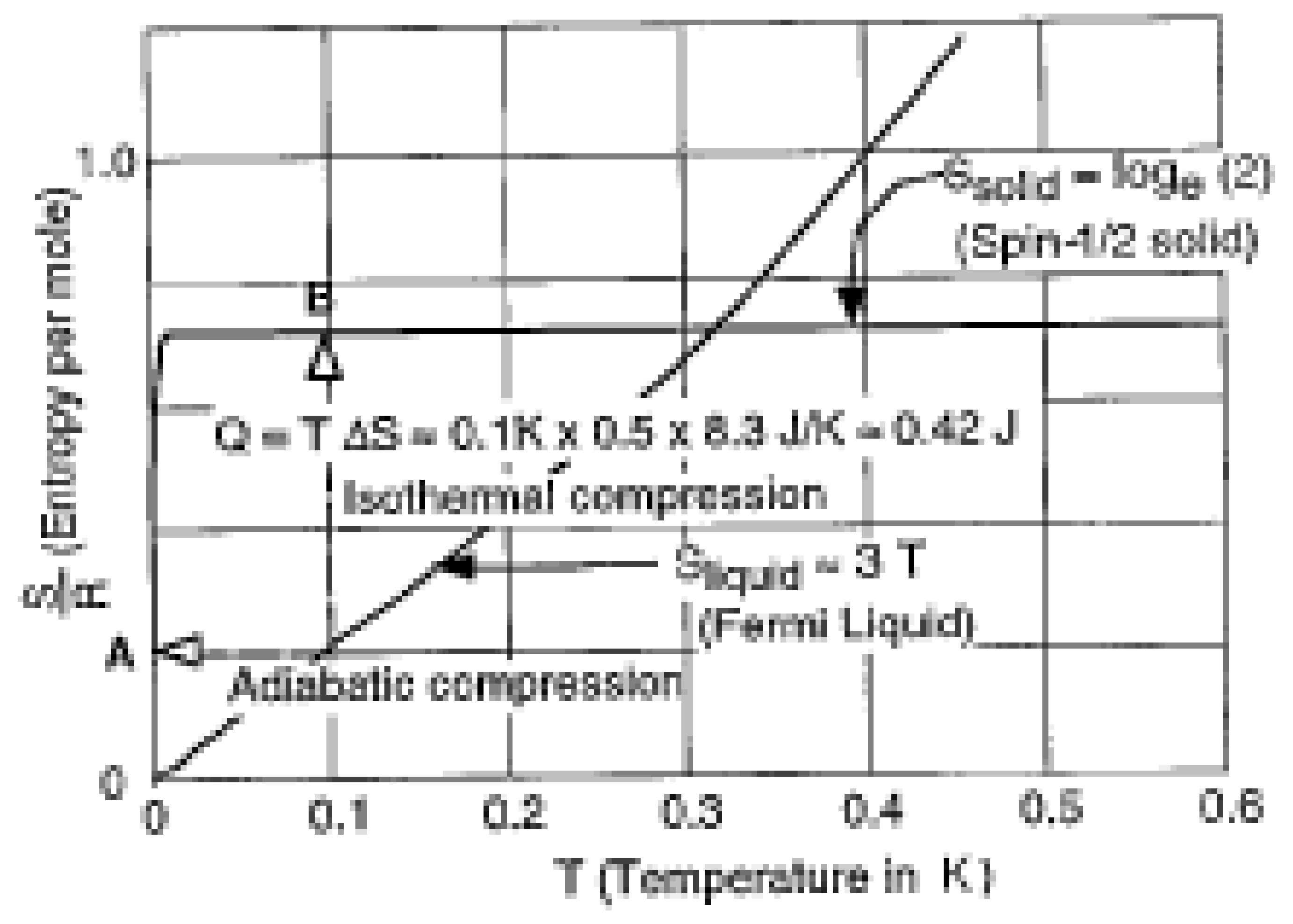
Clausius-Clapeyron equation

$$\left(\frac{dP}{dT}\right)_{melting} = \frac{S_{liquid} - S_{solid}}{V_{liquid} - V_{solid}}$$

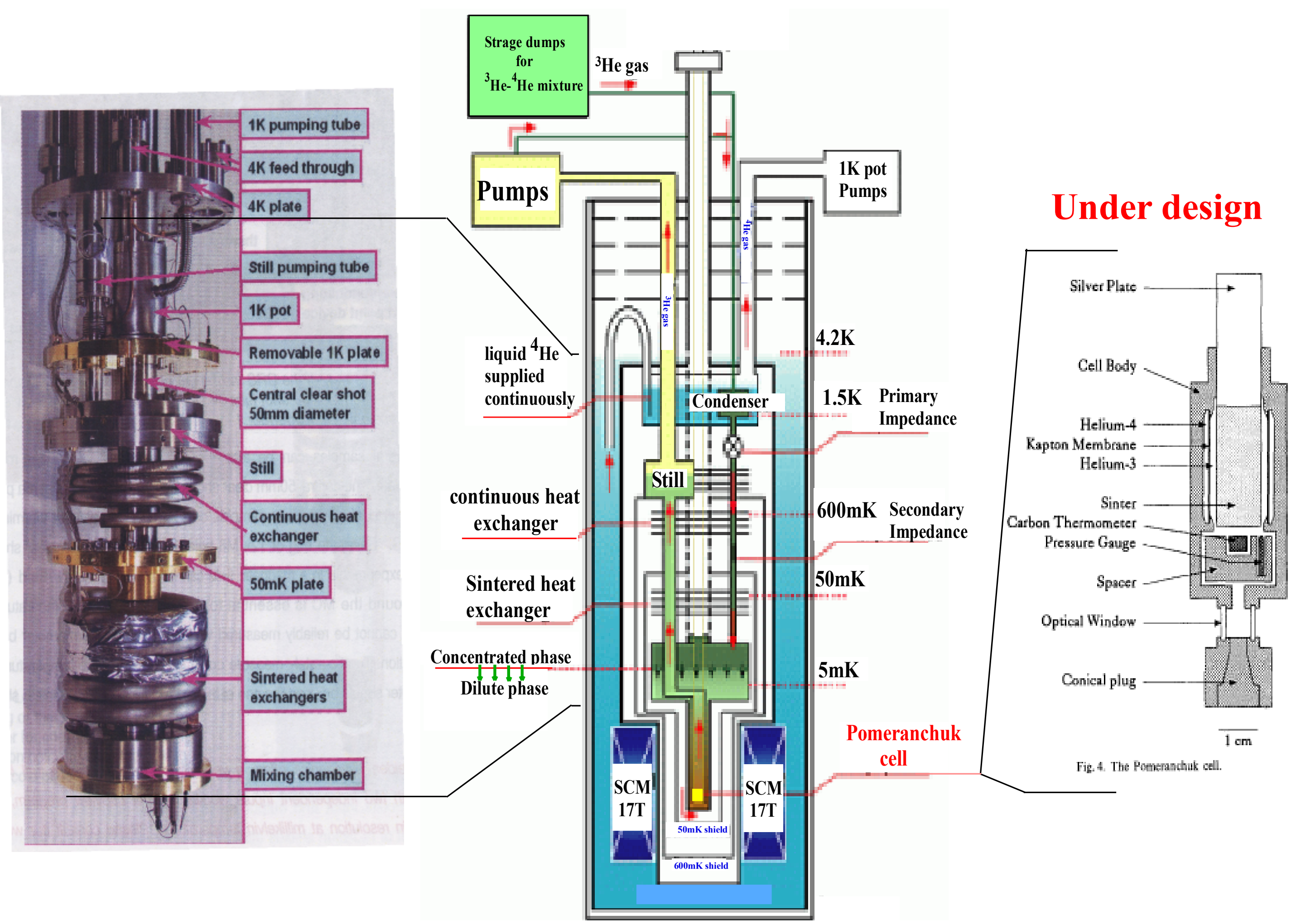
This suggests $S_{solid} > S_{liquid}$ at low T.



Therefore, the temperature would be lowered by solidification of liquid ^{3}He by pressure since the solidification brings an increase of entropy.

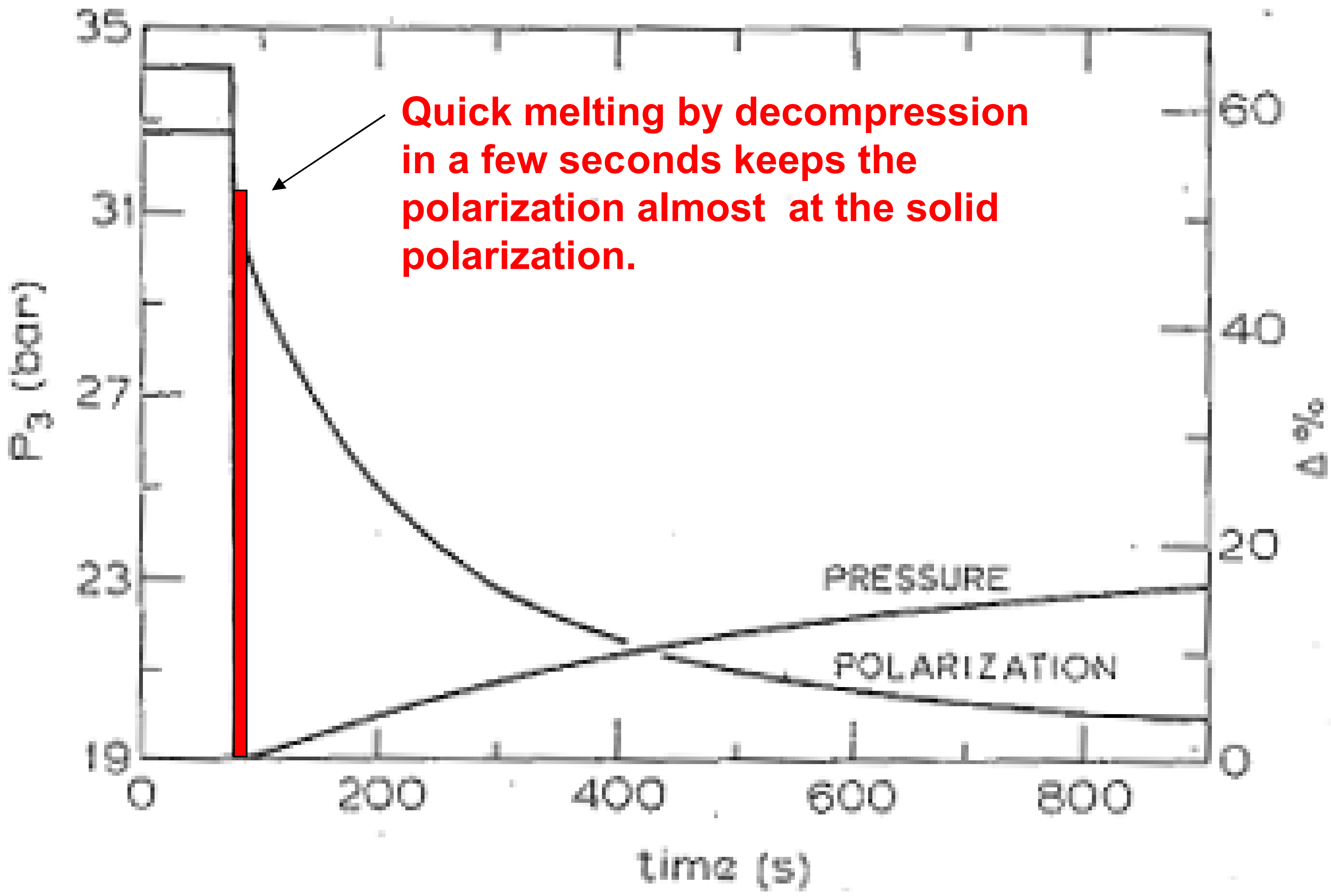


Pomeranchuk ^{3}He polarizer at RCNP, Osaka



^{3}He-^{4}He Dilution refrigerator
Leiden/Osaka/Orsay

Expected performance
Lowest Temperature: 5 mK
Cooling Power 3000 μW at T = 120 mK
15 μW at T = 12 mK



Quick melting by decompression in a few seconds keeps the polarization almost at the solid polarization.

4.3. NMR/MRI of other hyperpolarized nuclei

4.3.1 ^{129}Xe-MRI promising

- **Lipophilia:**

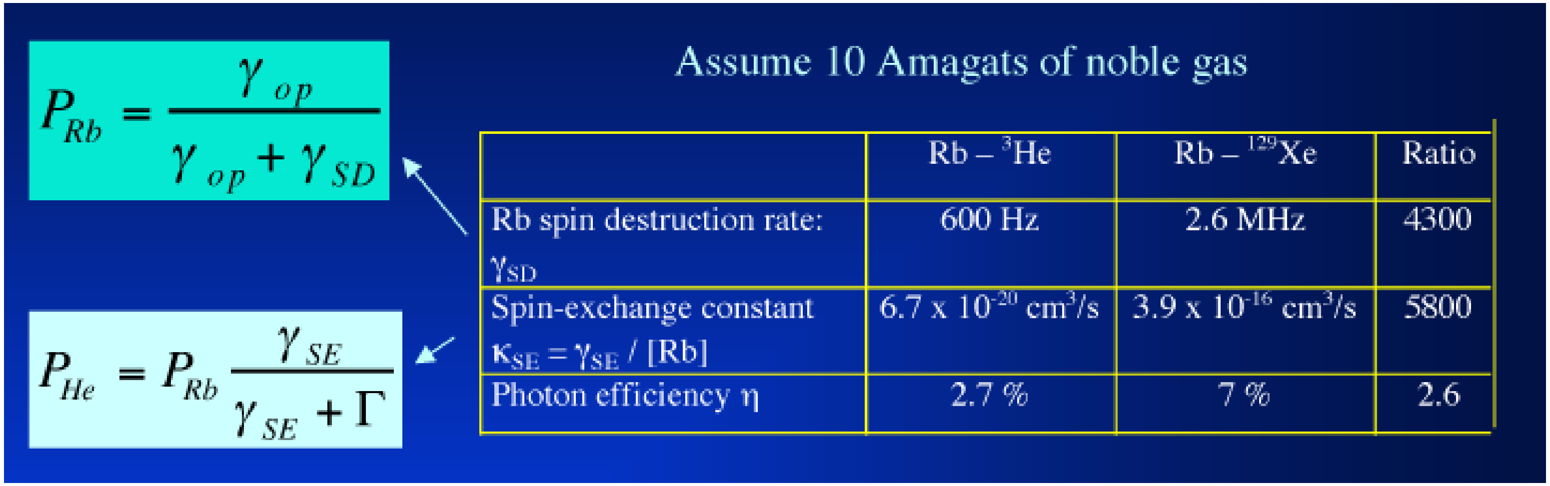
  Unlike helium or water, it is readily absorbed by fatty tissue.

- **Large chemical shifts:**

  Chemical shifts larger than H can be exploited to identify biochemical details in magnetic resonance imaging.

- **Method of polarization - SEOP**

  But, significant difference of SEOP exists between ^{3}He and ^{129}Xe.



$$P_{Rb} = \frac{\gamma_{op}}{\gamma_{op} + \gamma_{SD}}$$

$$P_{He} = P_{Rb} \frac{\gamma_{SE}}{\gamma_{SE} + \Gamma}$$

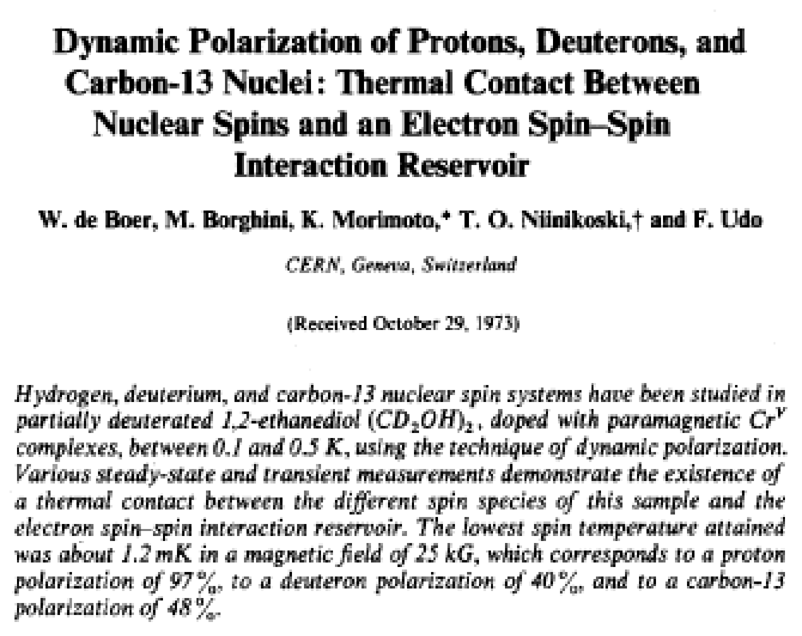
Assume 10 Amagats of noble gas

	Rb – ^{3}He	Rb – ^{129}Xe	Ratio
Rb spin destruction rate: γ_{SD}	600 Hz	2.6 MHz	4300
Spin-exchange constant $\kappa_{SE} = \gamma_{SE} / [Rb]$	6.7×10^{-20} cm^3/s	3.9×10^{-16} cm^3/s	5800
Photon efficiency η	2.7 %	7 %	2.6

- Rb is much harder to polarize in the presence of Xe
- ^{129}Xe polarizes much more promptly than ^{3}He

4.3.2. Hyperpolarized ^{13}C, ^{15}N, and ^{29}Si NMR by DNP (Dynamic Nuclear Polarization)

1973 CERN group (W. de Boer, T. O. Niinikoski et al.)



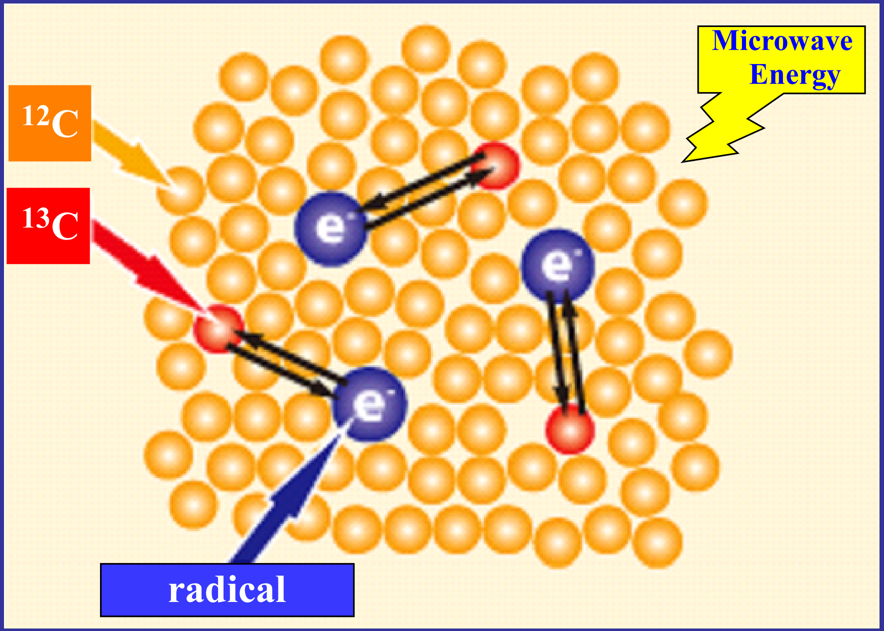
Dynamic Polarization of Protons, Deuterons, and Carbon-13 Nuclei: Thermal Contact Between Nuclear Spins and an Electron Spin–Spin Interaction Reservoir

W. de Boer, M. Borghini, K. Morimoto,* T. O. Niinikoski,† and F. Udo

CERN, Geneva, Switzerland

(Received October 29, 1973)

Hydrogen, deuterium, and carbon-13 nuclear spin systems have been studied in partially deuterated 1,2-ethanediol $(CD_2OH)_2$*, doped with paramagnetic* Cr^V *complexes, between 0.1 and 0.5 K, using the technique of dynamic polarization. Various steady-state and transient measurements demonstrate the existence of a thermal contact between the different spin species of this sample and the electron spin–spin interaction reservoir. The lowest spin temperature attained was about 1.2 mK in a magnetic field of 25 kG, which corresponds to a proton polarization of 97%, to a deuteron polarization of 40%, and to a carbon-13 polarization of 48%.*

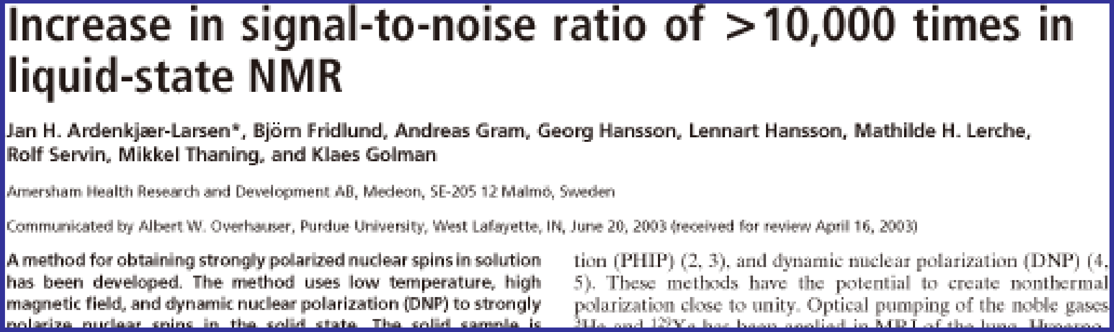


A partially deuterated 1,2-ethanediol [$(CD_2OH)_2$] doped with paramagnetic Cr^V was dynamically polarized

P(^{13}C) ~ 43%

with B =2.5 T, and T = 1.2 mK

1 Dutch and Swedish group (J. H. Andenkjaer-Larsen et al.) showed a striking result.



Increase in signal-to-noise ratio of >10,000 times in liquid-state NMR

Jan H. Ardenkjær-Larsen*, Björn Fridlund, Andreas Gram, Georg Hansson, Lennart Hansson, Mathilde H. Lerche, Rolf Servin, Mikkel Thaning, and Klaes Golman

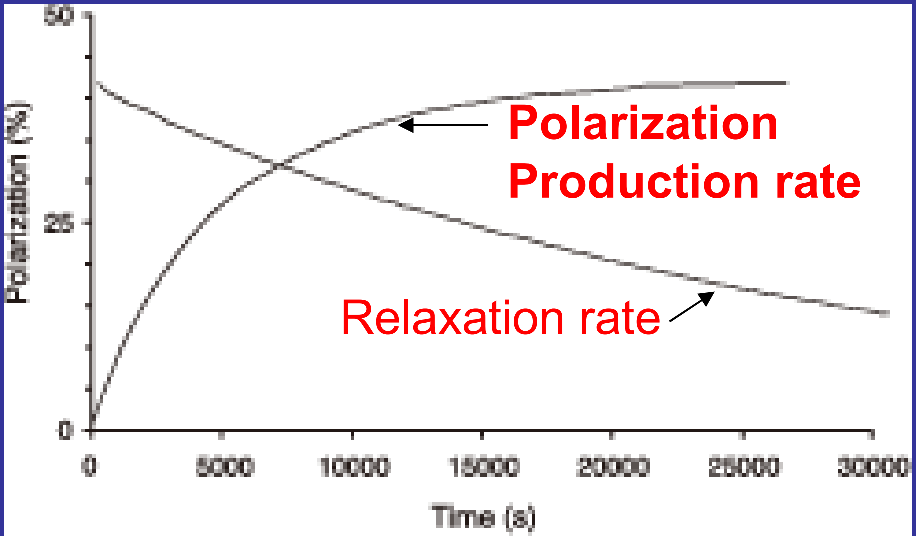
Amersham Health Research and Development AB, Medeon, SE-205 12 Malmö, Sweden

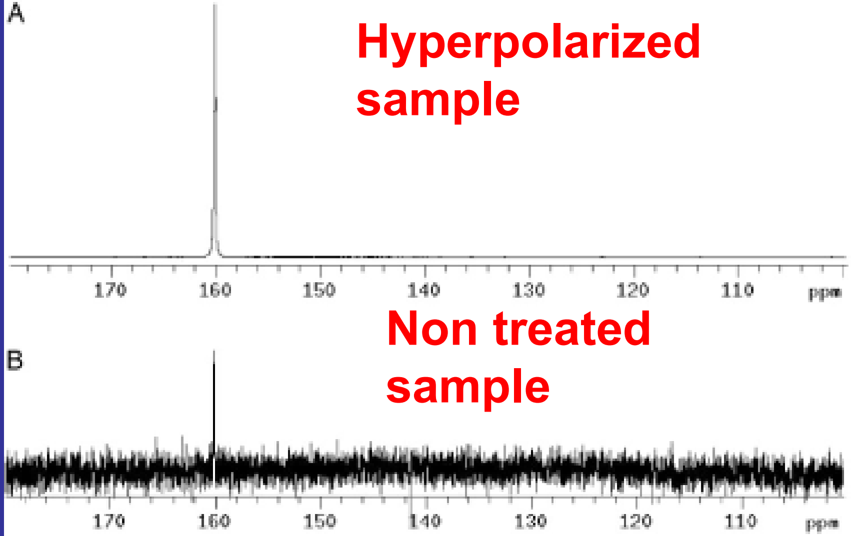
Communicated by Albert W. Overhauser, Purdue University, West Lafayette, IN, June 20, 2003 (received for review April 16, 2003)

A method for obtaining strongly polarized nuclear spins in solution has been developed. The method uses low temperature, high magnetic field, and dynamic nuclear polarization (DNP) to strongly

tion (PHIP) (2, 3), and dynamic nuclear polarization (DNP) (4, 5). These methods have the potential to create nonthermal polarization close to unity. Optical pumping of the noble gases

Aqueous [^{13}C] urea quickly dissolved from the solid phase hyperpolarized by the DNP method has open up a new frontier, where an enhanced NMR signal can be acquired, or a high sensitive agent for in vivo imaging or spectroscopy is required. P(^{13}C) ~ 37%, P(^{15}N) ~ 7.8% with B = 3.35T, T = 4.2 K





• Conclusion

- ☐ The history of hyperpolarized ^{3}He- and ^{129}Xe-MRI is very short. Actually, it started only 10 and a few years ago.
- ☐ However, their great validity has been proven particularly in the biomedical field.
- ☐ Their great success encourages in enhancing NMR signals of heavier isotopes such as ^{13}C and ^{15}N for biomedical use too.

Thanks for your
patient attention