Imaging applications:

Gamma emitters and magnetic resonance imaging contrast agents

Two main types of imaging:

(i) involving a radioactive tracer

(ii) magnetic resonance imaging

These imaging applications are diagnostic tools to see what is happening in the body.

Magnetic resonance imaging

Essentially NMR of the water in the tissues of the body. Humans are approx. 70% water.

As in NMR the patient is placed within a large superconducting magnet and pulsed with radiowaves (*c.f.* NMR machines 60MHz) and the resulting signals analysed by computer.

As with NMR:

MRI signal intensity depends on the relaxation time of the nuclei of the protons.

Slight modifications in relaxation time exhibit significant intensity increases.

There is relaxation time dependence on tissue water content which allows us to discriminate- giving the image.

...MRI...

Magnetic resonance imaging (MRI) is one of the newest **diagnostic medical** imaging technologies that uses **strong magnets** and **pulses of radio waves** to manipulate the **natural magnetic properties** in the body to generate a **visible image**.

Magnetic Resonance Angiography: study blood flow

Magnetic Resonance Spectroscopy: chemical composition of diseased tissue

Magnetic Resonance CholangioPancreatography: a non-invasive potential alternative for the diagnostic procedure endoscopic retrograde cholangiopancreatography

Advantages of MRI vs X-rays, Computed tomography scan (CT scan) and ultrasounds

1) Greater natural contrast

2) Very minor fluctuations in chemical composition can be determined,

3) It can distinguish fine variations in tissues deep within the body,

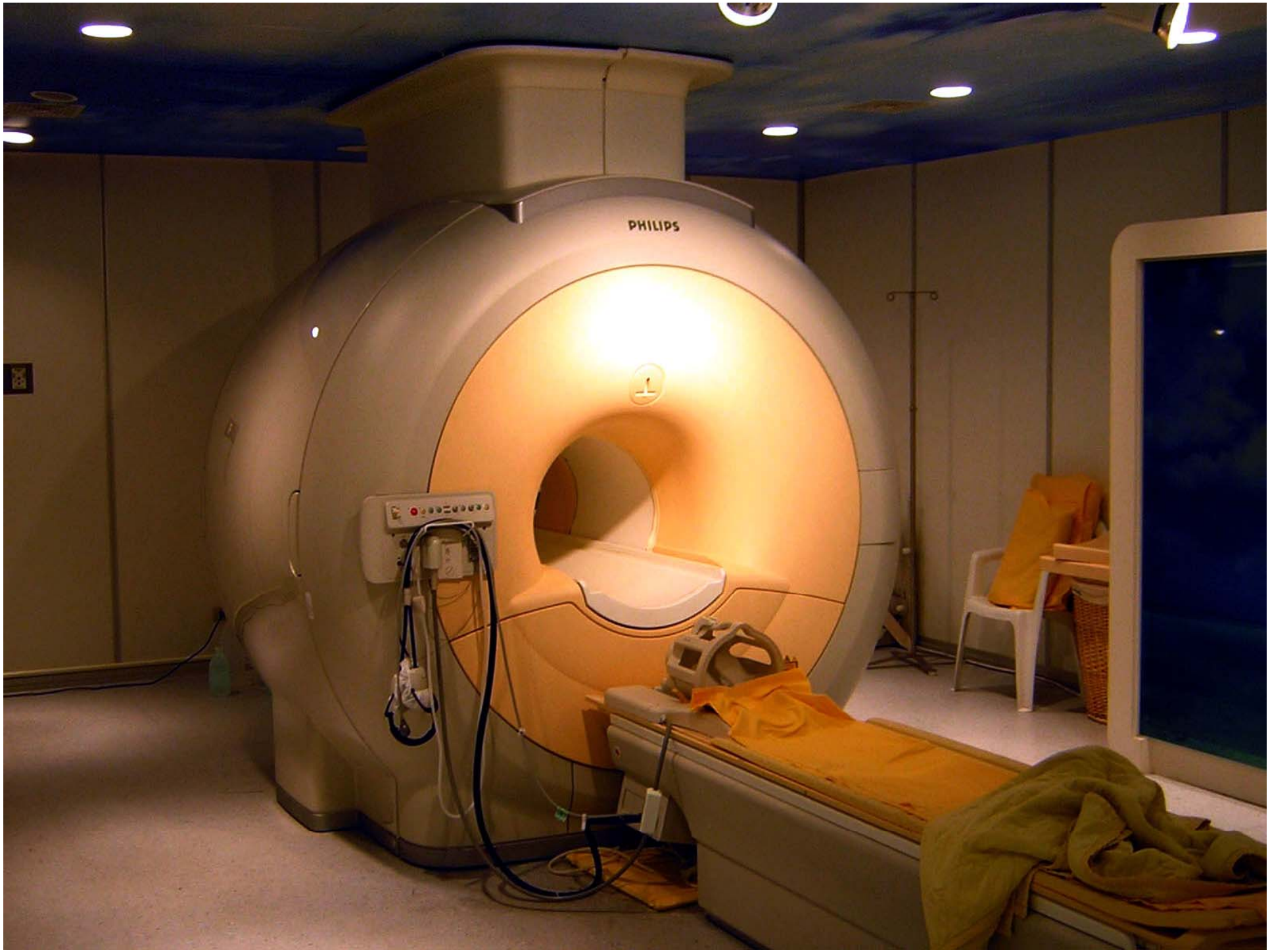
4) Useful for spotting and distinguishing diseased tissues (tumors and other lesions) early in their development,

5) The entire body can be scanned, from head to toe and from the skin to the deepest recesses of the brain,

6) MRI scans are not obstructed by bone, gas, or body waste,

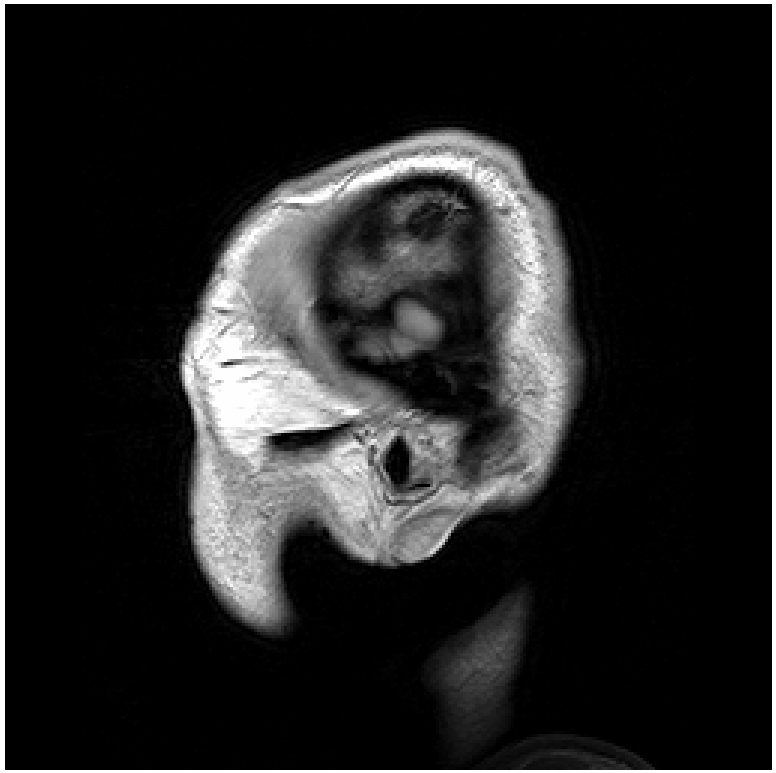
7) Safe…does not depend on potentially harmful ionizing radiation,

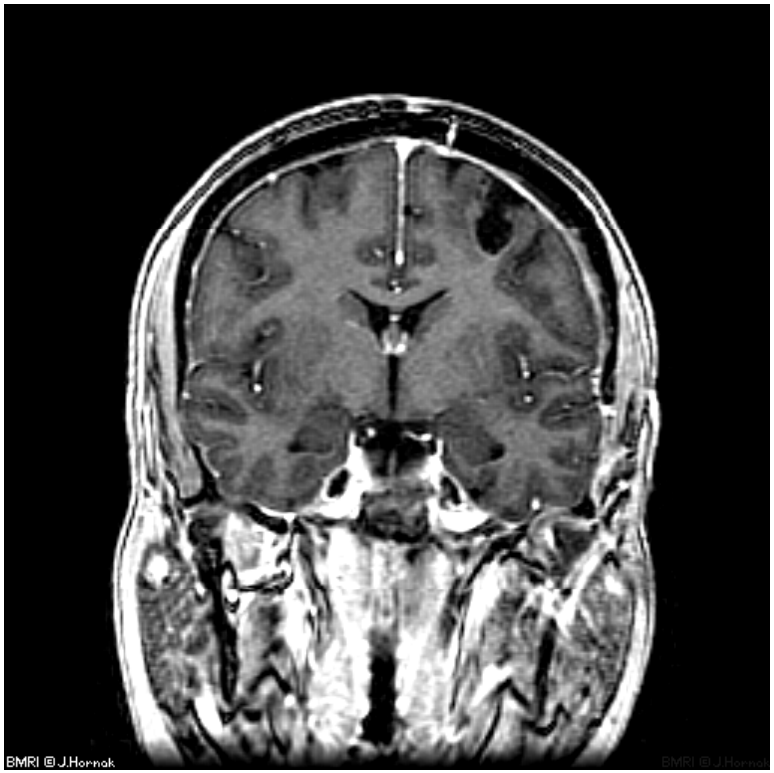
…BUT…rather complex procedure and…$$$...


PHILIPS

Where is it most commonly used?...Seeing is bieleving

1) **BRAIN AND HEAD.** It can see through bone (the skull) and deliver high-quality pictures of the brain's delicate soft tissue structures… brain tumor, stroke, or infection (meningitis), brain diseases (like Alzheimer's or Huntington's diseases, or multiple sclerosis), or when developmental retardation suggests a birth defect. MRI can also provide pictures of the sinuses and other areas of the head beneath the face..





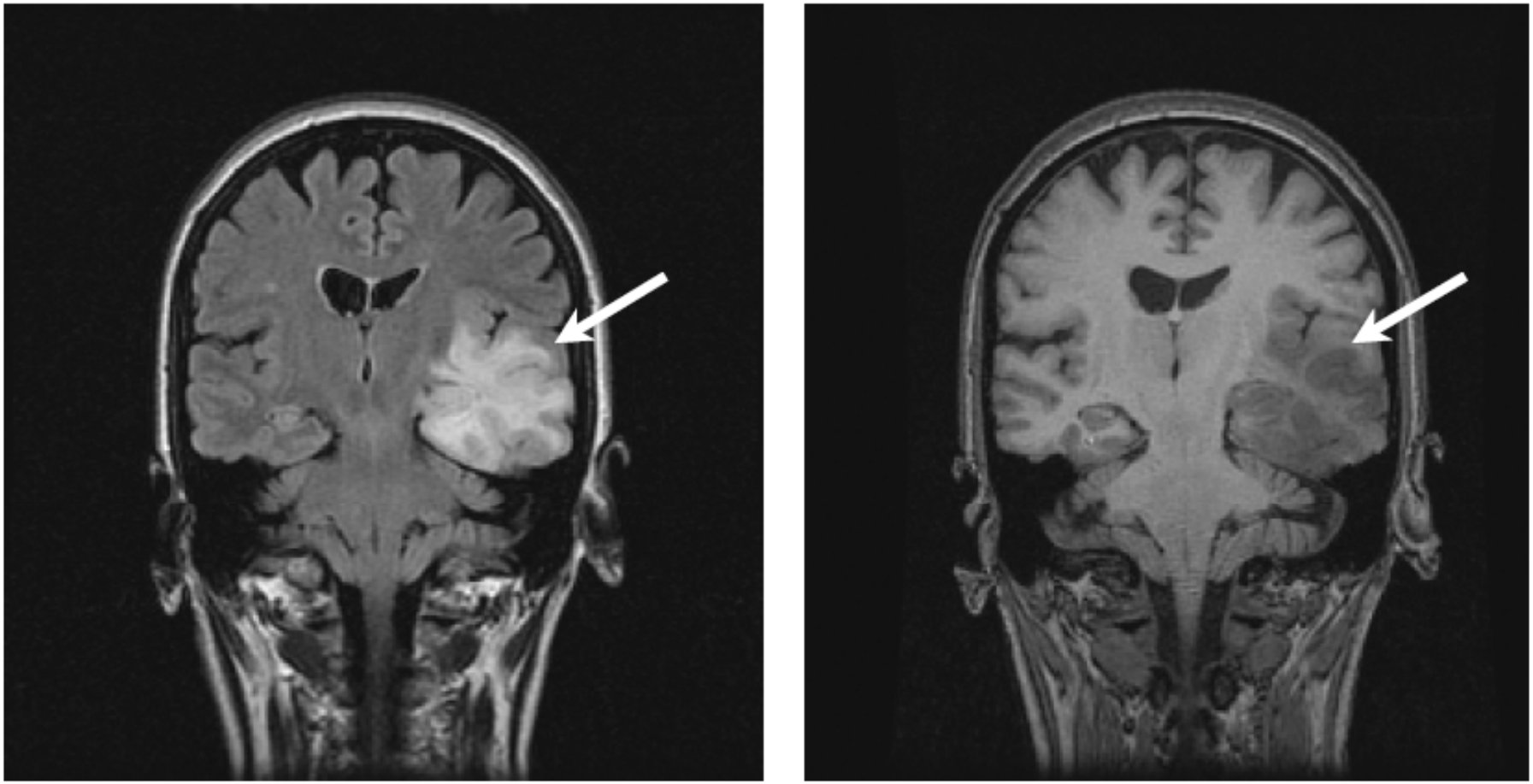
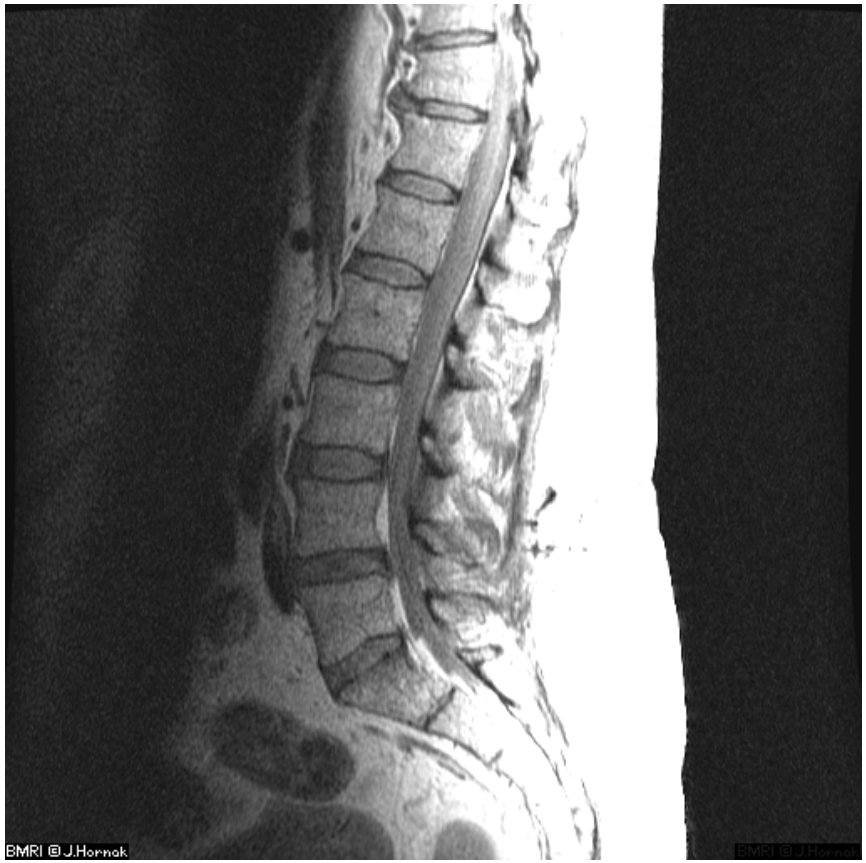
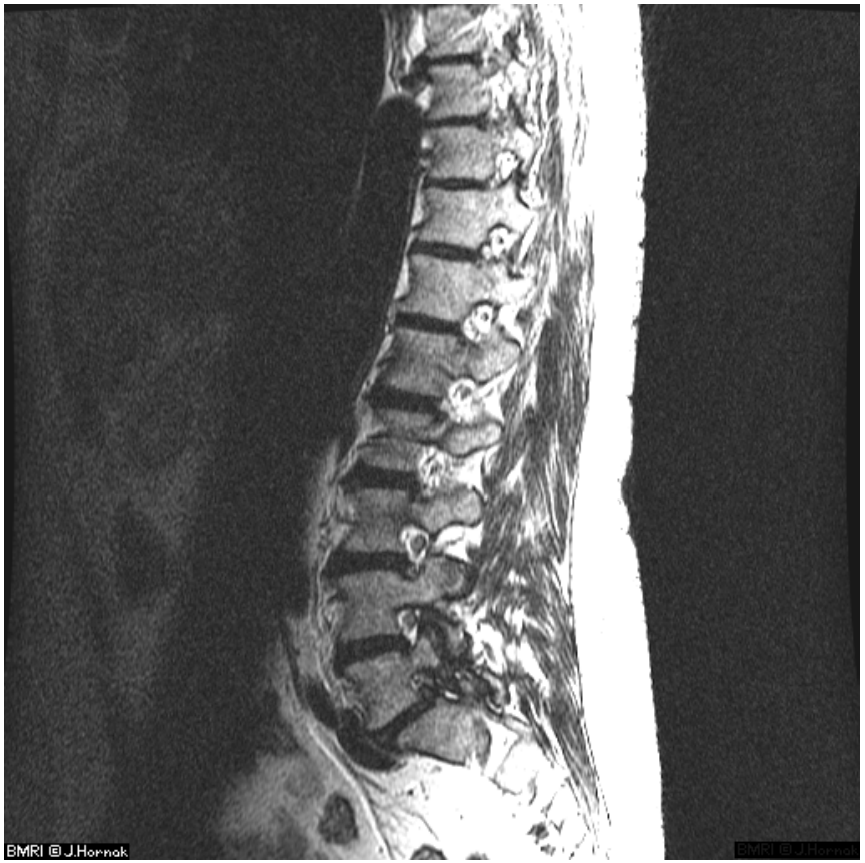


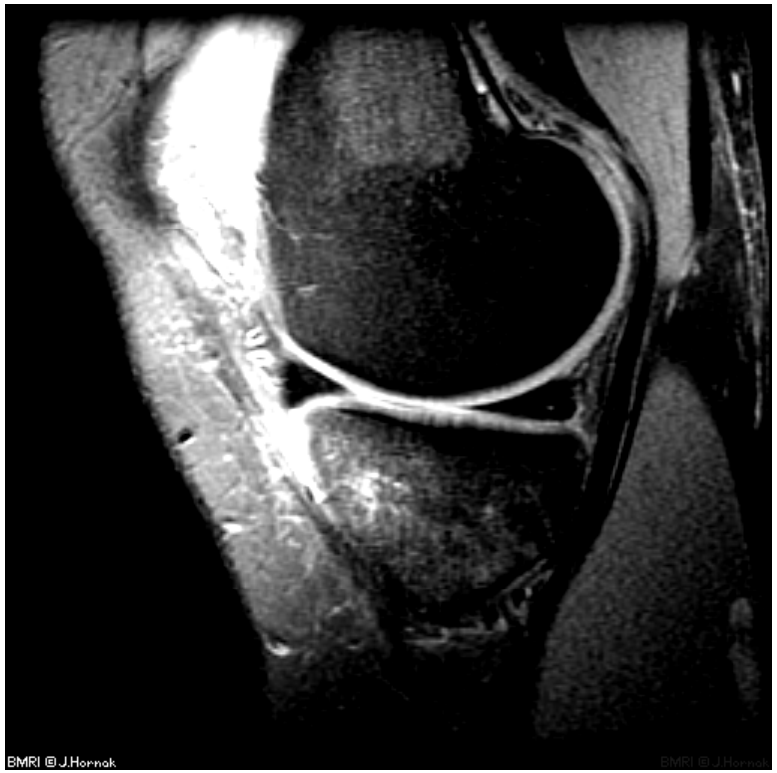
Figure 3.1 (a) Coronal image of the brain showing a tumour (arrow). In this image the tumour is bright against the darker grey of the normal brain tissue. (b) The same slice with a different pulse sequence, this time showing the tumour darker than the surrounding brain.

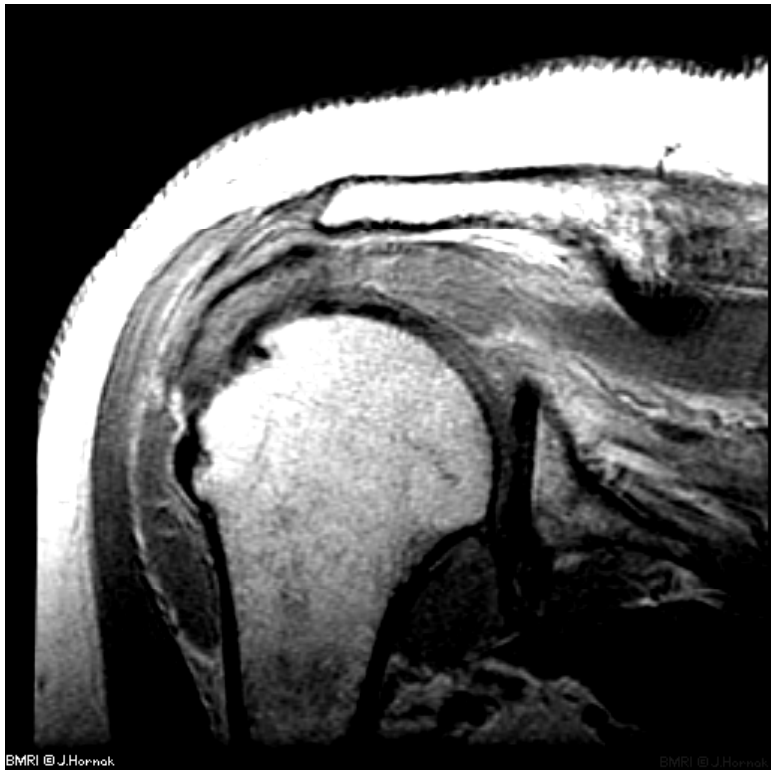
2) **SPINE**. Spinal problems can create a host of seemingly unrelated symptoms. MRI to identify and evaluate degenerated spinal discs. It can also be used to determine the condition of nerve tissue within the spinal cord.



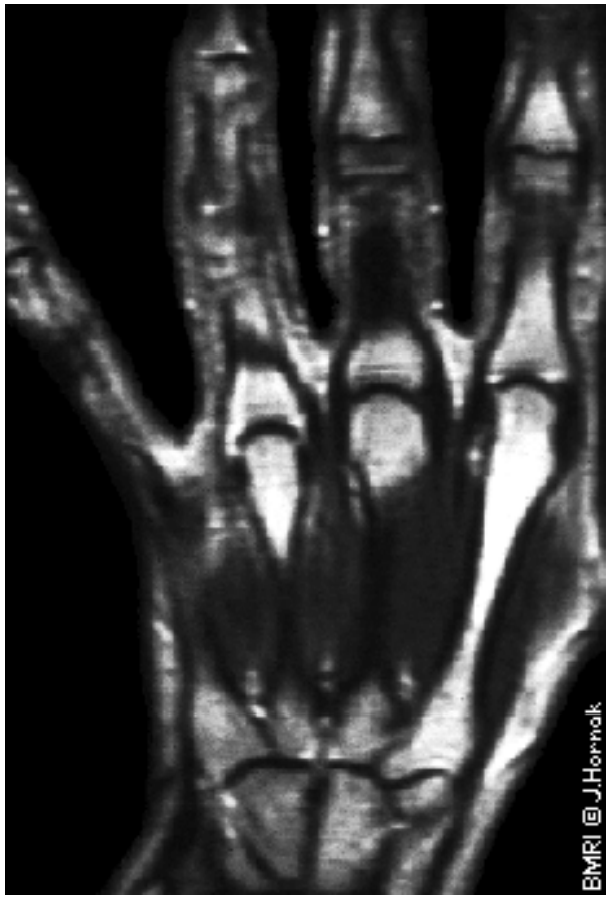


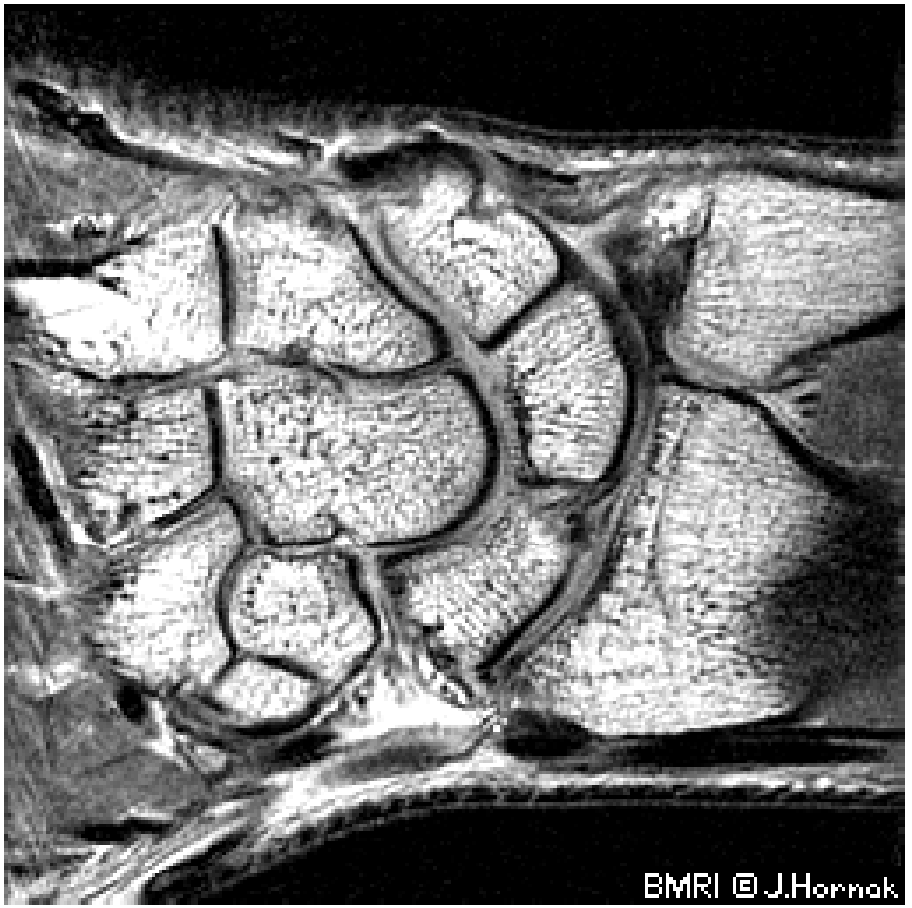
3) **JOINT**. Most commonly used…provide clear images of the bone, cartilage, ligament, and tendon that comprise a joint… diagnose joint injuries due to sports, advancing age, or arthritis…can also detect the presence of an otherwise hidden tumor or infection in a joint, and can be used to diagnose the nature of developmental joint abnormalities in children.



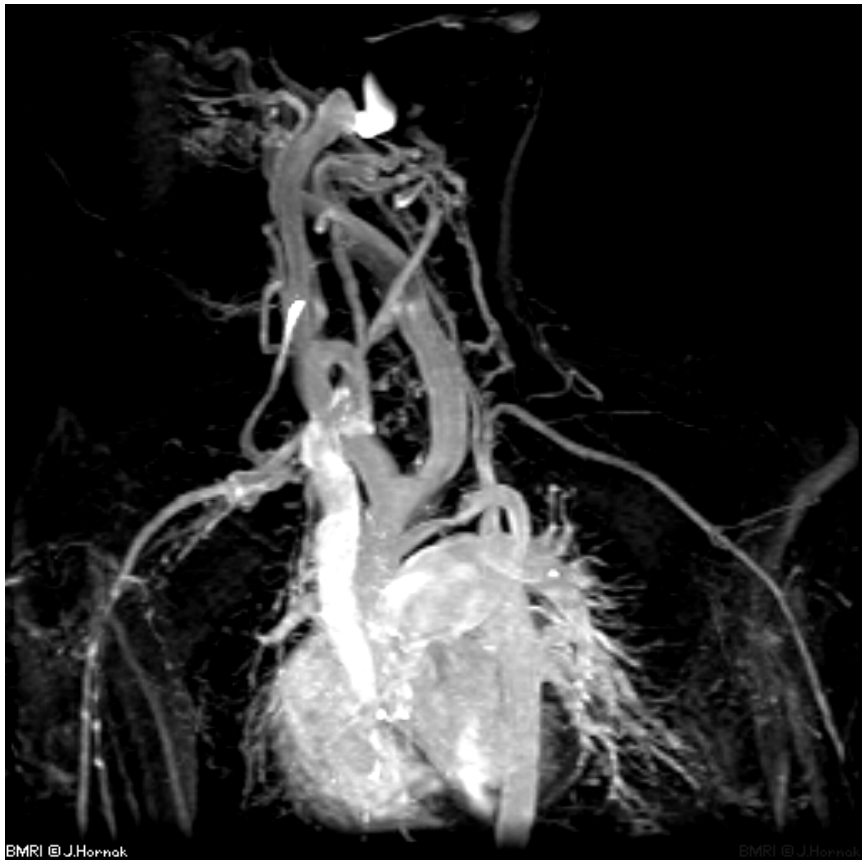


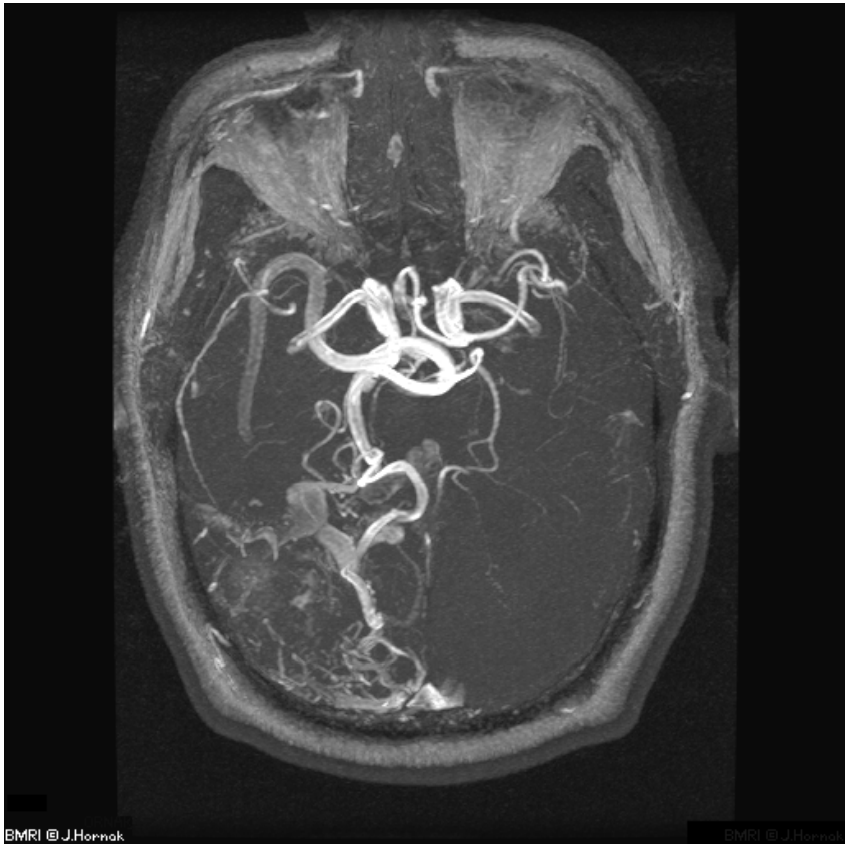
4) **SKELETON**…Since it can see through the skull it can also view the inside of bones …it can be used to detect bone cancer, inspect the marrow for leukemia and other diseases, assess bone loss (osteoporosis), and examine complex fractures.





5) **HEART AND CIRCULATION.** MRI technology can be used to evaluate the circulatory system. The heart and blood flow provides a good natural contrast medium that allows structures of the heart to be clearly distinguished





Timeline of MRI…how did it all begun???

1946: **Felix Bloch & Edward Purcell** discovered the Magnetic Resonance phenomenon (Nobel Prize 1952)

1971: Raymond Damadian showed that the nuclear magnetic relaxation times of tissues and tumors differed…!!!

1973: X-ray based CT is introduced by Hounsfield…

1973: **Paul Lauterbur** starts perfoming MRI exprs. in small tubes…(Nobel Prize in Medicine, 2003)

1975: **Richard Ernst** proposed MRI using phase and frequency encoding, and FT (Nobel Prize in Chemistry, 1991)…

1977: **Peter Mansfield** developed the echo-planar imaging (EPI) technique. This technique will be developed in later years to produce images at video rates (Nobel Prize in Medicine, 2003)

1980: Edelstein demonstrated imaging of the body using Ernst's technique…

1987: Charles Damoulin magnetic resonance angiography (MRA), which allowed imaging of flowing blood

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Figure 1.5 Nobel prize-winners in NMR: (a) Purcell 1912–1997, (b) Bloch 1901–1999, (c) Bloembergen b. 1920, (d) Ernst b. 1933, (e) Lauterbur b. 1929 and (f) Mansfield b. 1933. Courtesy of the Nobel Museum.

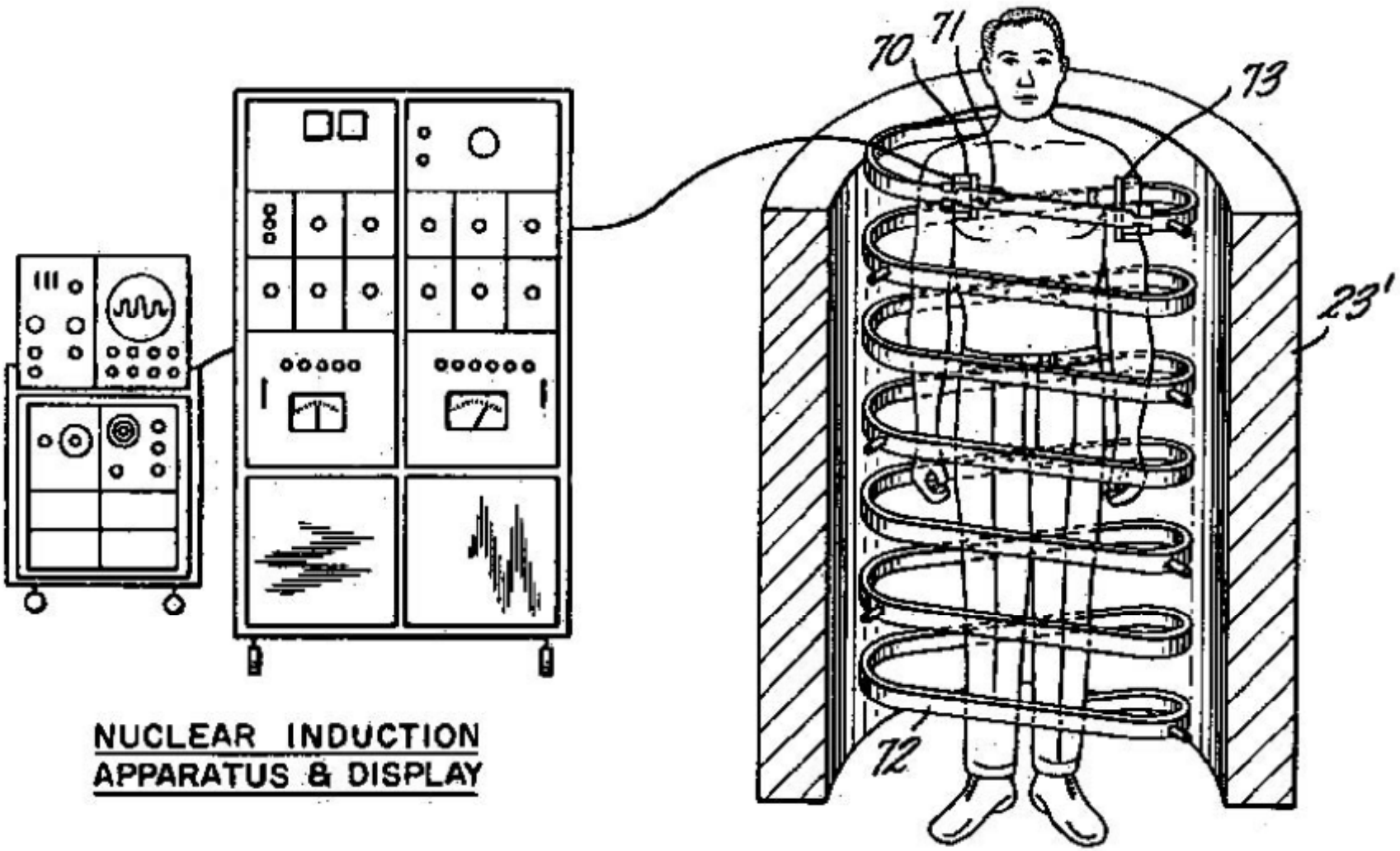


Figure 1.2 Raymond Damadian's "Apparatus and method for detecting cancer in tissue". US patent 3789832 filed 17 March 1972, issued 5 February 1974. Image from the US Patent and Trademark Office.

Where do we stand today???

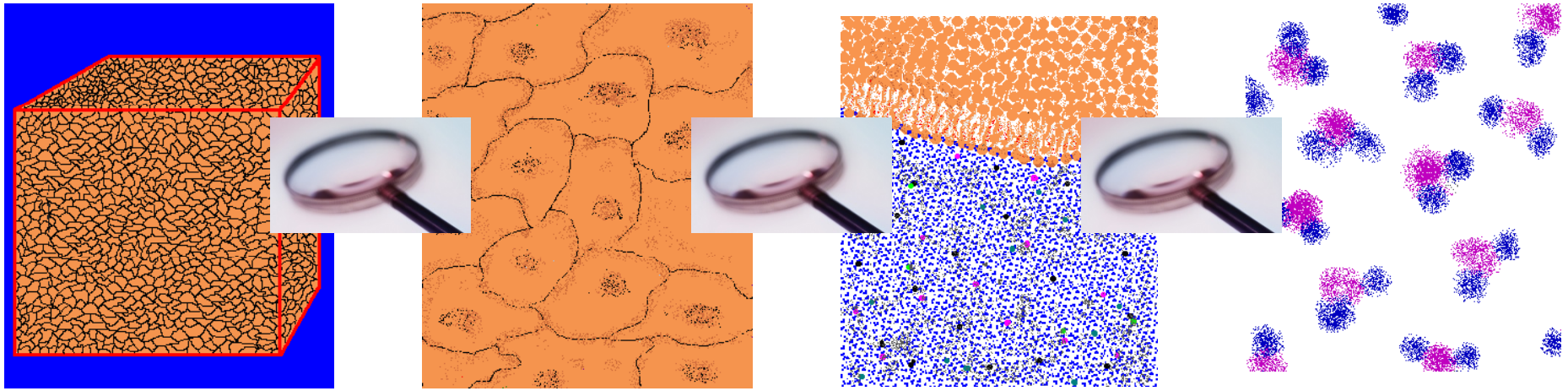
There are approximately 10.000 MRI units worldwide (2003) and ~ 75.000.000 MRI scans are performed annually…!!!

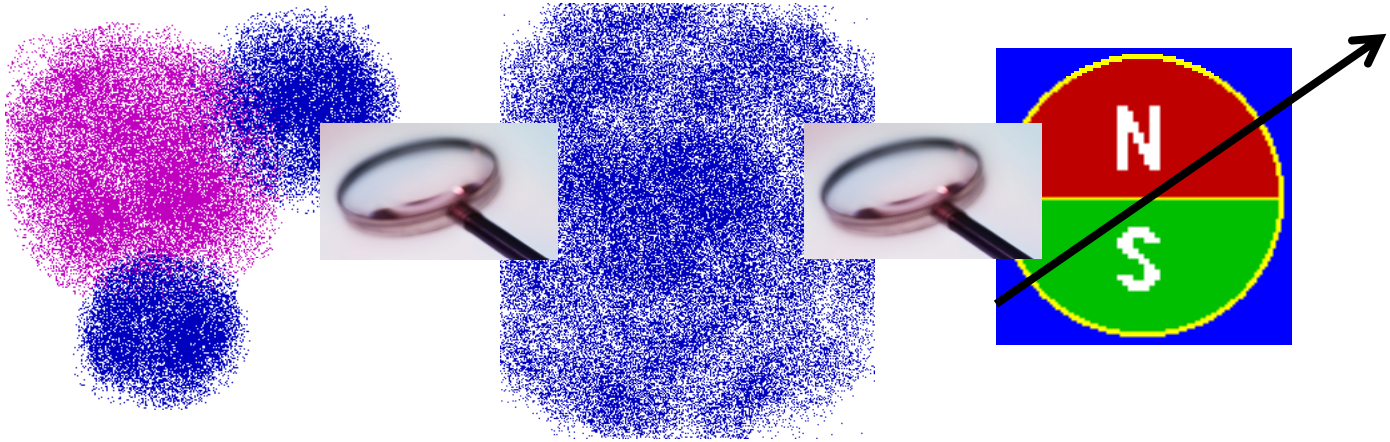
…Combines: chemistry, physics, engineering…including superconductivity, cryogenics, quantum physics, digital and computer science…

Well…how does it work?

Ohh…not chemistry again !

The human body is primarily fat and water. Fat and water have many hydrogen atoms which make the human body approximately 63% hydrogen atoms. Hydrogen nuclei have an NMR signal. For these reasons magnetic resonance imaging primarily images the NMR signal from the hydrogen nuclei





…will produce an NMR signal…!!!!

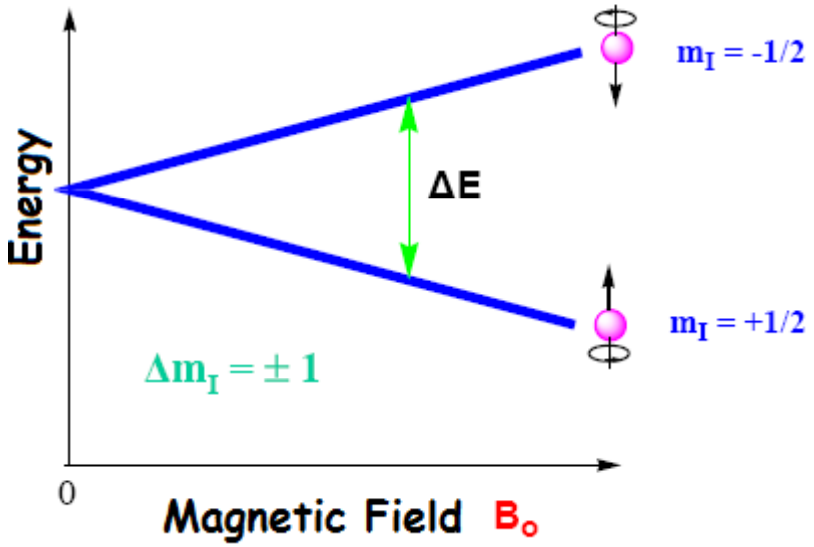
Spin Physics…I

Do you remember anything from Nuclear Magnetic Resonance???

What is "spin" ??? …a fundamental property of nature like electrical charge or mass. …multiples of 1/2 and can be + or -. Protons, electrons, and neutrons possess spin. Individual unpaired electrons, protons, and neutrons each possesses a spin of 1/2.

^{2}H: 1p, 1n and 1 e^- … total electronic spin= ½ and total nuclear spin=1

Think of a spin as an arrow...↑…when placed inside an external magnetic field, ↑ B, there will be 2 possibilities of the arrow: parallel and antiparrallel with B, ↑ ↑B and ↑↓B, the 2nd being higher in energy.



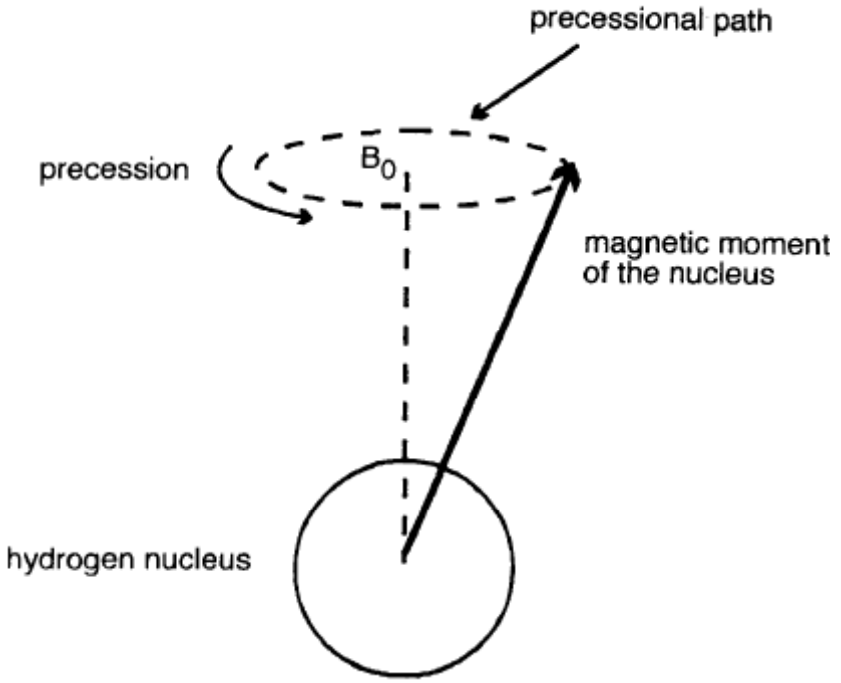
When we place a radiowave source, it can absorb a photon and see a **TRANSITION** between the 2 states…the frequency of the photon is $\nu = \gamma \cdot B$ (γ= gyromagnetic ratio).

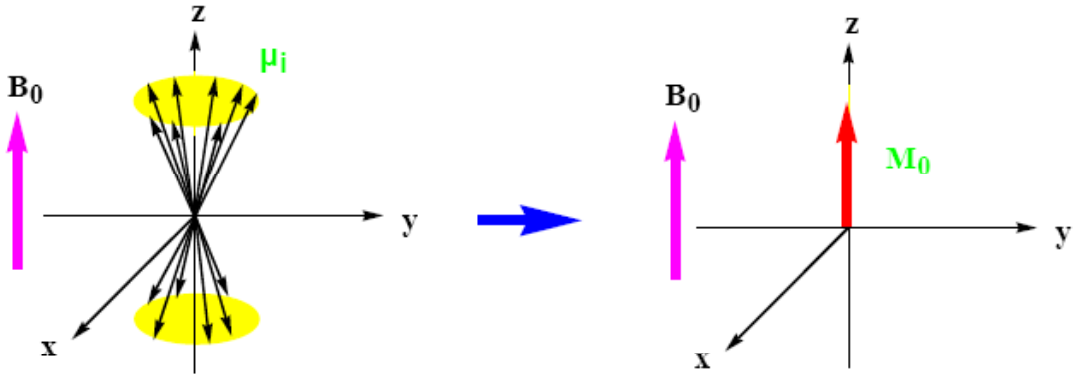
$\Delta E = h \cdot \nu$

$\nu = \gamma \cdot B$

$\Delta E = h \cdot \gamma \cdot B$

ν = Larmor Frequency





the precessional frequency (ω_0) = $B_0 \times \gamma$

B_0 is the magnetic field strength of the magnet, and

γ is the gyro-magnetic ratio. The gyro-magnetic ratio expresses the relationship between the angular momentum and the magnetic moment of each MR active nucleus. It is constant and is expressed as the precessional frequency of a specific MR active nucleus at 1.0 T. The unit of the gyro-magnetic ratio is therefore MHz/T.

M_0 : **Net Magnetization**….describes the whole spin population…and not each spin individually…

- The magnetic moment of hydrogen is called the *net magnetisation vector (NMV)*.
- The static external magnetic field is called B_0.
- The interaction of the NMV with B_0 is the basis of MRI.
- The unit of B_0 is tesla or gauss. 1 tesla (T) is the equivalent of 10 000 gauss (G).

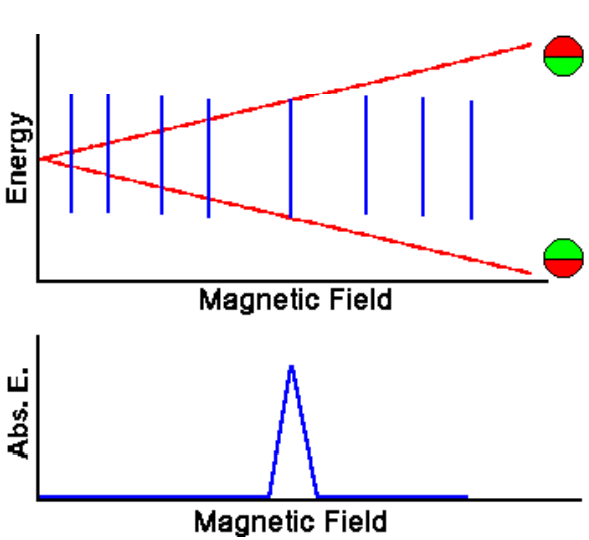
Larmor Frequency

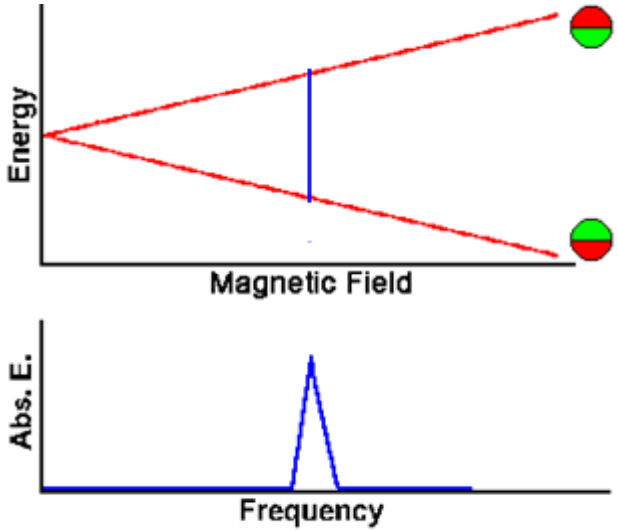
the precessional frequency (ω_0) = $B_0 \times \gamma$

at 1.5 T the precessional frequency of hydrogen is 63.86 MHz
(42.57 MHz × 1.5 T),
at 1.0 T the precessional frequency of hydrogen is 42.57 MHz
(42.57 MHz × 1.0 T),
at 0.5 T the precessional frequency of hydrogen is 21.28 MHz
(42.57 MHz × 0.5 T).

CW NMR Experiment

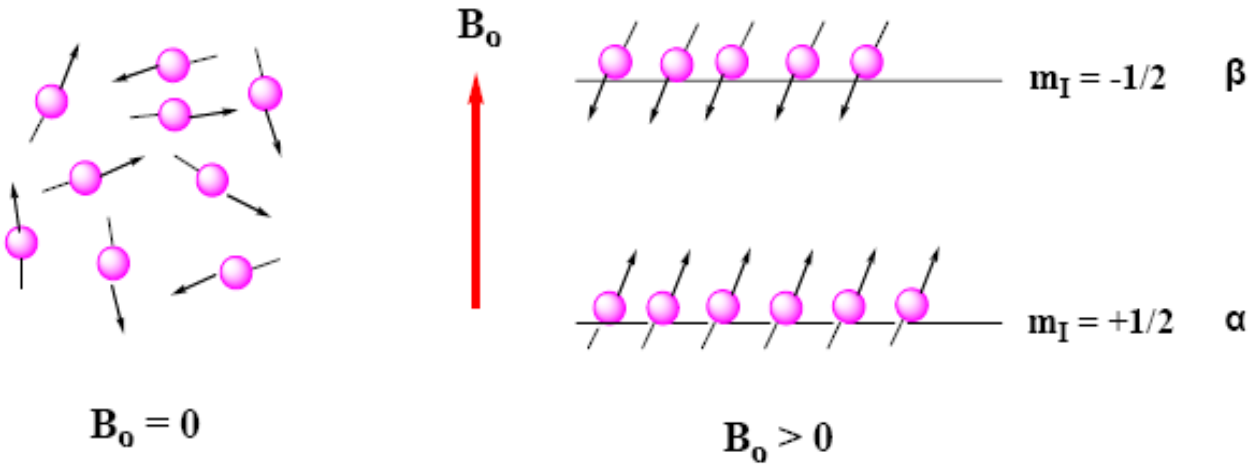
The simplest NMR experiment is the continuous wave (CW) experiment. There are two ways of performing this experiment. In the first, a constant frequency, which is continuously on, probes the energy levels while the magnetic field is varied.





The CW experiment can also be performed with a constant magnetic field and a frequency which is varied. The magnitude of the constant magnetic field is represented by the position of the vertical blue line in the energy level diagram.

Boltzmann Statistics….eh??

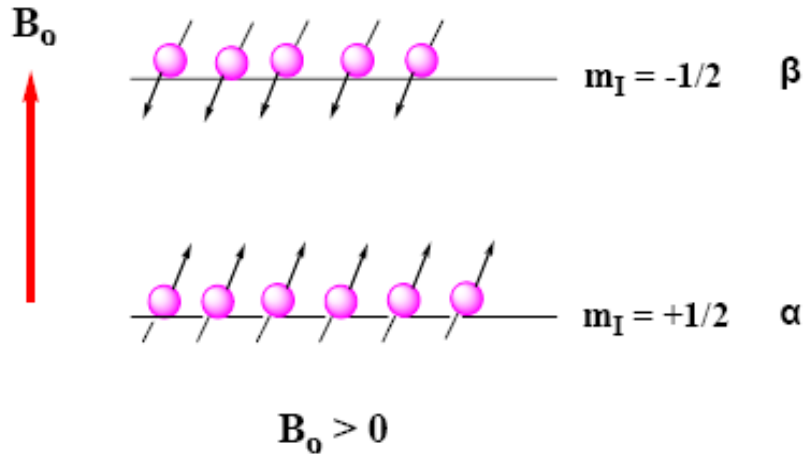


$$N_\alpha / N_\beta = e^{\Delta E / kT} = e^{\gamma \hbar B_0 / kT}$$

$$N_\alpha + N_\beta = 1$$

k : Boltzmann's constant, 1.3805×10^{-23} J/Kelvin;

At RT: $N_\alpha > N_\beta$ (slightly),
T↓=> N_α/N_β↑ .....as T increases N_α/N_β approaches 1.



Signal in NMR: 1) due to the TRANSITIONS from α → β, and β → α

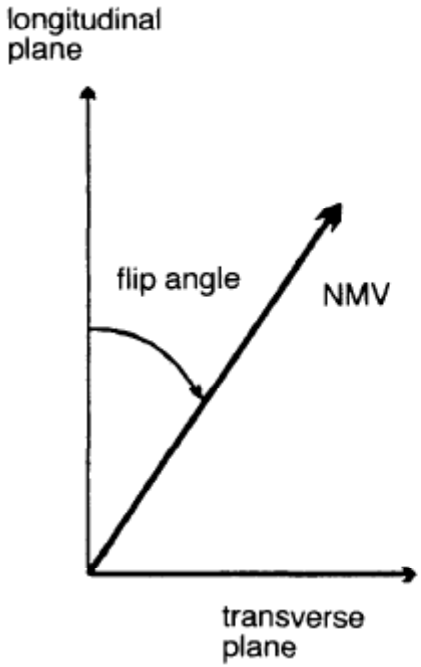
2) proportional to the population difference between a and b

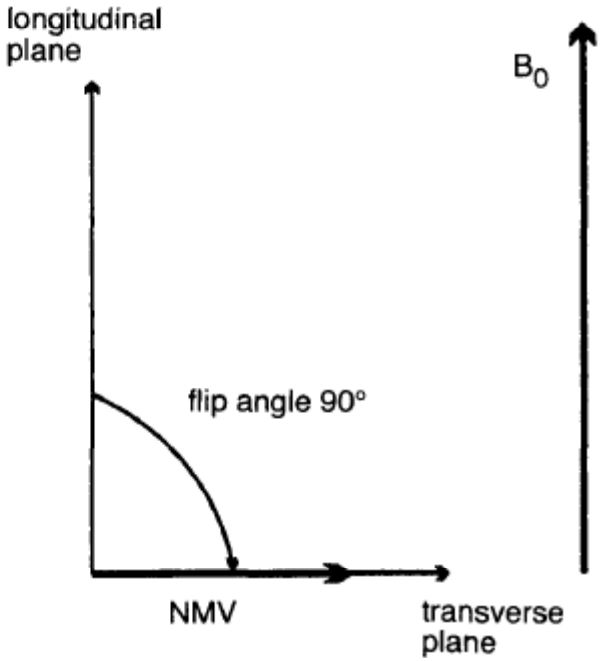
KEY FACTOR : natural abundance **AND** biological abundace of the isotope…

Element	Symbol	Natural Abundance
Hydrogen	^{1}H	99.985
	^{2}H	0.015
Carbon	^{13}C	1.11
Nitrogen	^{14}N	99.63
	^{15}N	0.37
Sodium	^{23}Na	100
Phosphorus	^{31}P	100
Potassium	^{39}K	93.1
Calcium	^{43}Ca	0.145

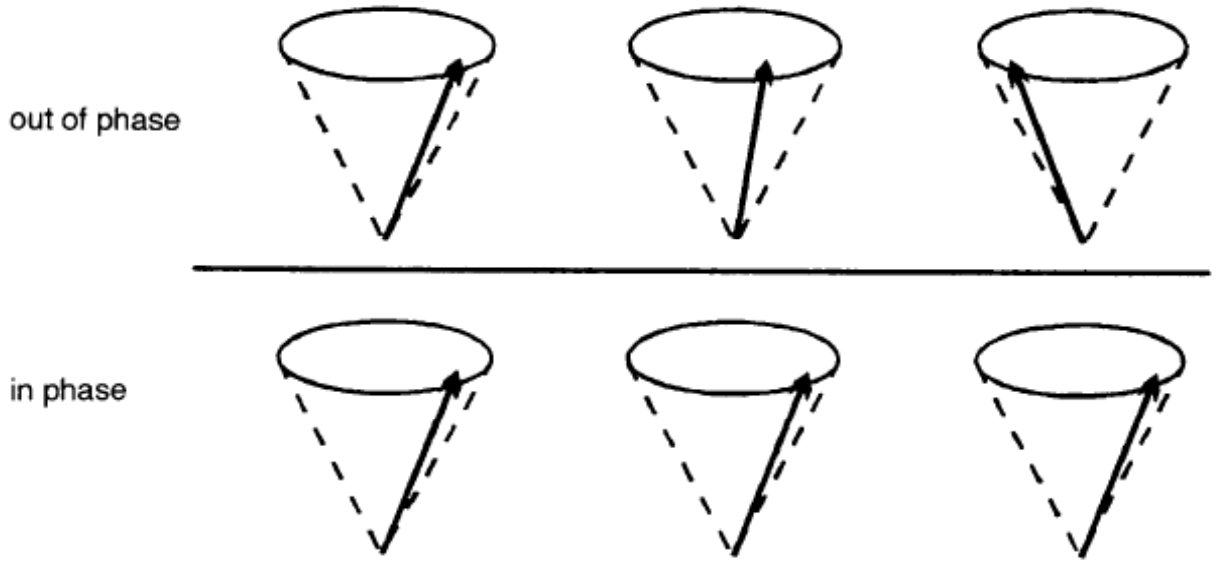
Element	Biological Abundance*
Hydrogen (H)	0.63
Sodium (Na)	0.00041
Phosphorus (P)	0.0024
Carbon (C)	0.094
Oxygen (O)	0.26
Calcium (Ca)	0.0022
Nitrogen (N)	0.015

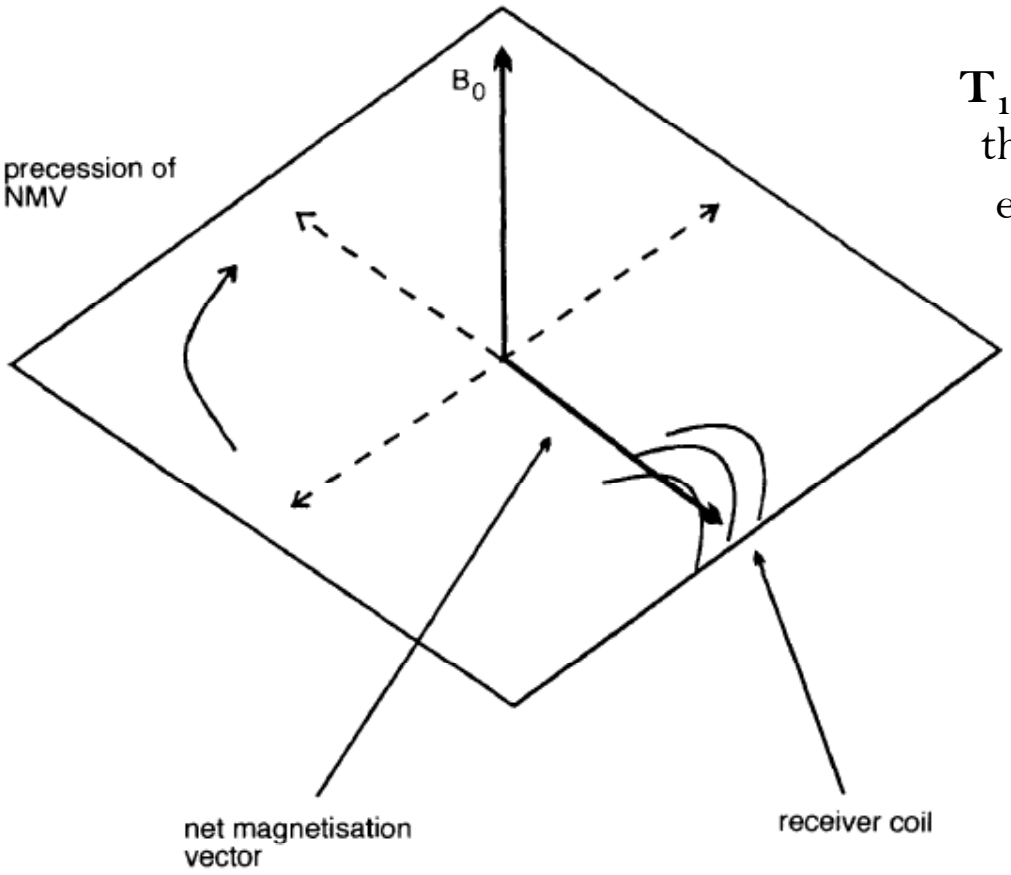
Relaxation, Recovery and Decay





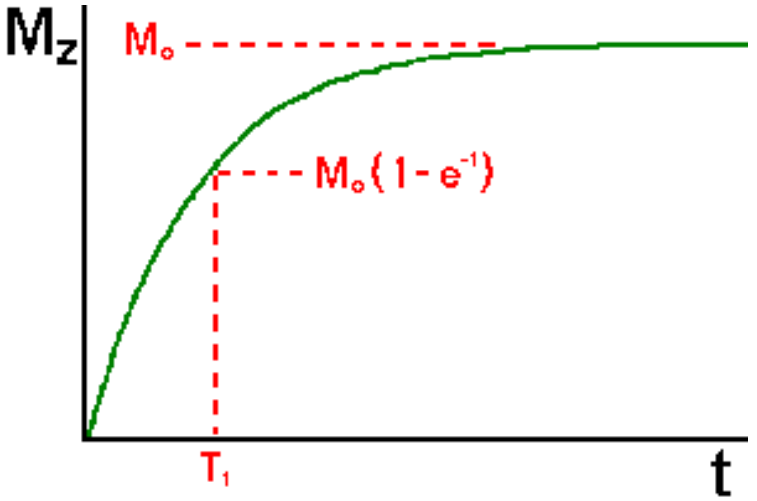
- For resonance of hydrogen to occur, RF at exactly the Larmor frequency of hydrogen must be applied.
- The result of resonance is an NMV in the transverse plane that is in phase.
- This NMV precesses in the transverse plane at the Larmor frequency.





$\mathbf{T_1}$ is the time to reduce the difference between the **longitudinal** magnetization (M_Z) and its equilibrium value by a factor of e (or 63%).

$$M_z = M_o \left(1 - e^{-t/T1} \right)$$



The free induction decay signal (FID)

When the RF pulse is switched off, the NMV is again influenced by B_0 and it tries to realign with it. In order to do so, the NMV must lose the energy given to it by the RF pulse. The process by which the NMV loses this energy is called *relaxation*. As relaxation occurs, the NMV returns to realign with B_0.

- The amount of magnetisation in the longitudinal plane gradually increases – this is called *recovery*.

and at the same time but independently

- The amount of magnetisation in the transverse plane gradually decreases – this is called *decay*.

As the magnitude of transverse magnetisation decreases, so does the magnitude of the voltage induced in the receiver coil. The induction in reduced signal is called the *free induction decay (FID)* signal.

T_1 process: Spin-lattice Relaxation T_1

In **specific** cases:

- If **M** has been tilted into the *xy* plane, then $M_z(0) = 0$ and the recovery is simply

$$M_z(t) = M_{z,\mathrm{eq}}\left(1 - e^{-t/T_1}\right)$$

i.e. the magnetisation recovers to 63% of its equilibrium value after one time constant T_1.

- In the inversion recovery experiment, commonly used to measure T_1 values, the initial magnetisation is inverted, $M_z(0) = -M_{z,\mathrm{eq}}$, and so the recovery follows

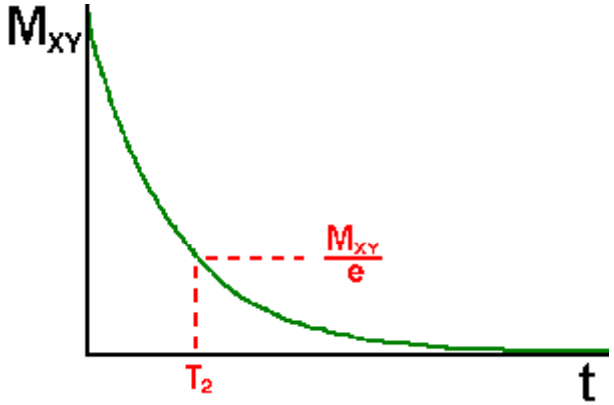
$$M_z(t) = M_{z,\mathrm{eq}}\left(1 - 2e^{-t/T_1}\right)$$

…involves an interaction with the surroundings

T_2 process: Spin-Spin Relaxation T_2

If we tilt M_0 on the xy plane, then: the time constant which describes the return to equilibrium of the transverse magnetization, M_{XY}, is called the spin-spin relaxation time, T_2.

$$M_{XY} = M_{XY0}\, e^{-t/T2}$$



Key Factor for T_2:
Spin-spin interactions…

T_2 is always less than or equal to T_1.

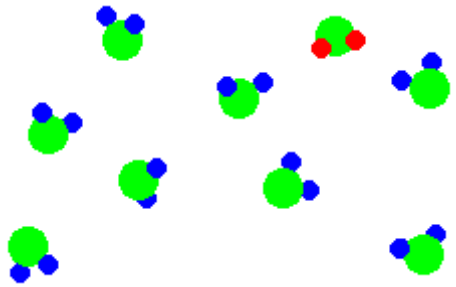
…WHAT TO REMEMBER…

The net magnetization in the XY plane goes to zero and then the longitudinal magnetization grows in until we have M_o along Z

If we "hit" M_0 with a magnetic pulse on the xy plane, then:
The relationship between the rotation angle in radians (q)and the length, in seconds, that the B_1 field is applied (t)is:

$$q = 2p\ t\ B_1 g$$

Spin Relaxation…make ends meet



Motions in solution which result in time varying magnetic fields cause spin relaxation

Time varying fields at the Larmor frequency cause transitions between the spin states and hence a change in M_Z…

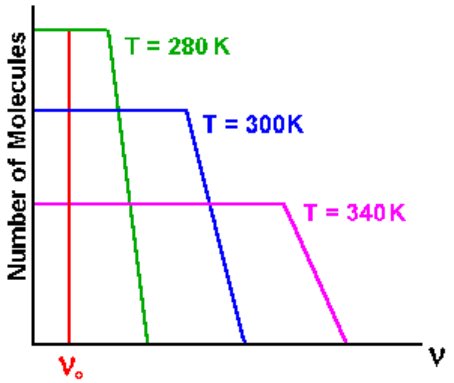
There is a distribution of rotation frequencies in a sample of molecules. Only frequencies at the Larmor frequency affect T_1.

Larmor freq. ~ B_0…so then $T_1=f(B_0)$

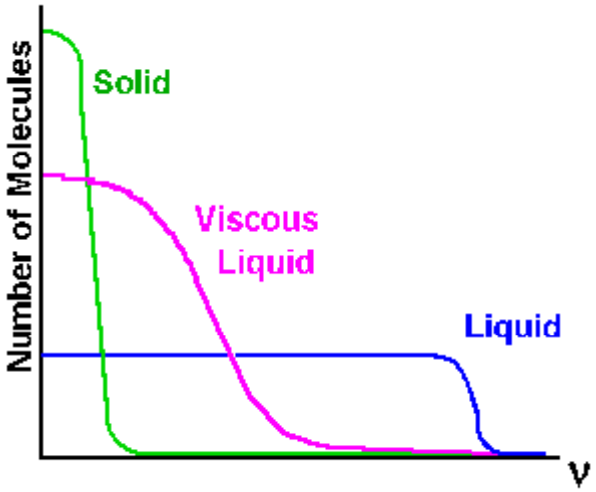
T_1 is inversely proportional to the density of molecular motions at the Larmor frequency.

The rotation frequency distribution depends on the temperature and viscosity of the solution. Therefore T_1 will vary as a function of temperature.

NOT big thing for human body….VERY SMALL temperature dif…so not dif. T_1 due to temperature



The **viscosity does** however vary significantly
from tissue to tissue and influences T_1 …



Questions and Problems…so far!

1) Many magnetic resonance imagers operate at a magnetic field strength of 1.5 Tesla. A few research units operate at 4.7 Tesla. What is the resonance frequency of the following nuclei in each of the magnetic fields?

^{1}H

^{23}Na

^{31}P

2) What is the energy of the photon that will be absorbed by a ^{1}H nucleus in a 1.5 Tesla magnetic field? How does this compare in energy to a $2x10^{19}$ Hz x-ray photon?

Given: $g(^{1}H)=42.58$ MHz/T

$g(^{23}Na)= 11.27$ MHz/T

$g(^{31}P)= 17.25$ MHz/T

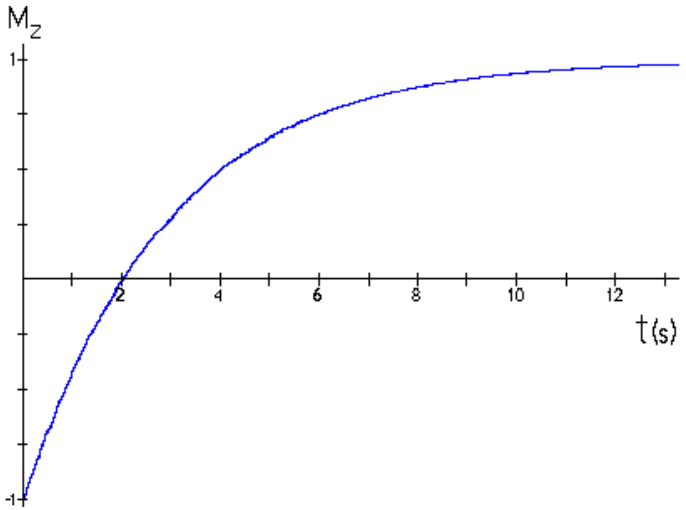
$h= 6.626x10^{-34}$ Js

3) A sample has a T_1 of 1.0 seconds. If the net magnetization is set equal to zero, how long will it take for the net magnetization to recover to 98% of its equilibrium value

4) A sample has a T_2 of 100 ms. How long will it take for any transverse magnetization to decay to 37% of its starting value?

5) A hydrogen sample is at equilibrium in a 1.5 Tesla magnetic field. A constant B_1 field of $1.17x10^{-4}$ Tesla is applied along the +x'-axis for 50 microseconds. What is the direction of the net magnetization vector after the B_1 field is turned off ???

6) Estimate the spin-lattice relaxation time constant based on the following plot of $M_z(t)$.



7) A sample has a T_1 of 0.8 seconds. The net magnetization from the sample set equal to zero and then allowed to recover towards its equilibrium value. After 1.0 seconds, what fraction of the equilibrium magnetization value will be present?

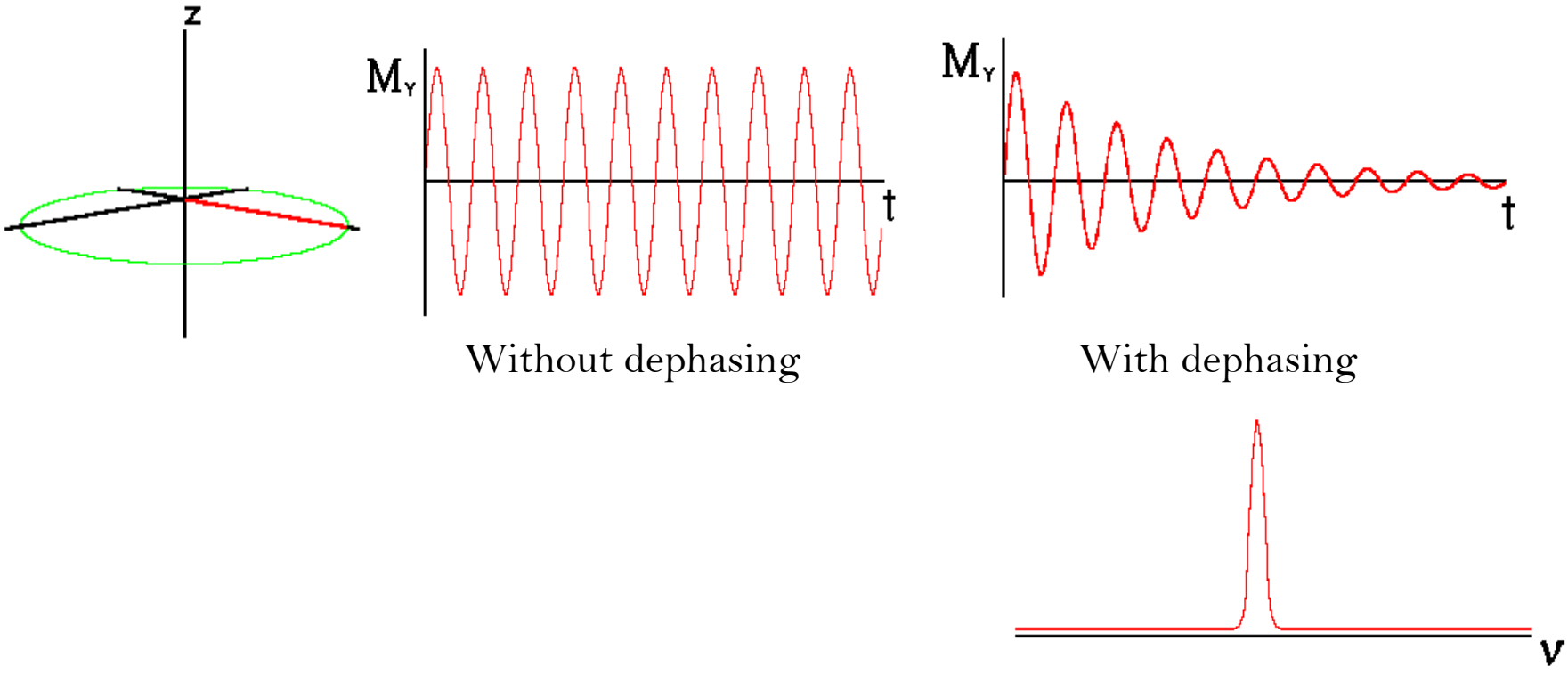
8) A sample has a T_2 of 50 ms. The net magnetization is rotated into the xy-plane and allowed to decay. Who much transverse magnetization will be present 20 ms after being placed in the plane?

9) A hydrogen sample is at equilibrium in a 1.5 Tesla magnetic field. A constant B_1 field of 2.34×10^{-4} Tesla is applied along the +x'-axis for 25 microseconds. What is the direction of the net magnetization vector after the B_1 field is turned off?

a bit further down the NMR trail…just a bit!

Things do not always work they way they should…T_2 is really T_2^* due to…
"dephasing of the spin packets" reasons

As transverse magnetization rotates about the Z axis, it will induce a current in a coil of wire located around the X axis. Plotting current as a function of time gives a sine wave. This wave will decay with time constant T_2^* This signal is called a free induction decay (FID)

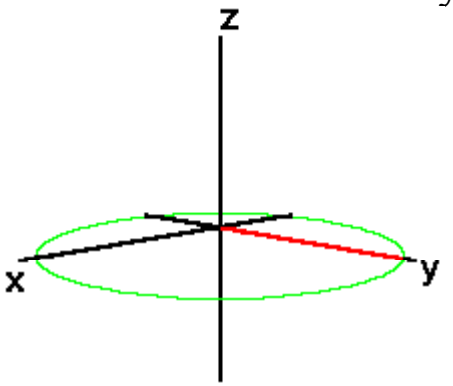


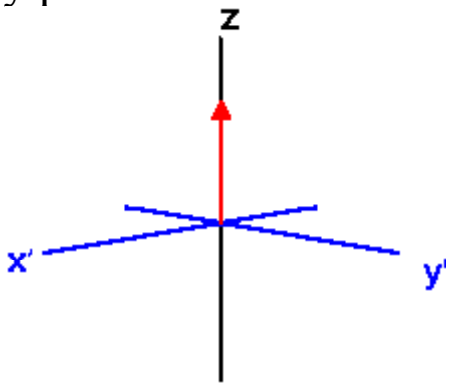
Without dephasing

With dephasing

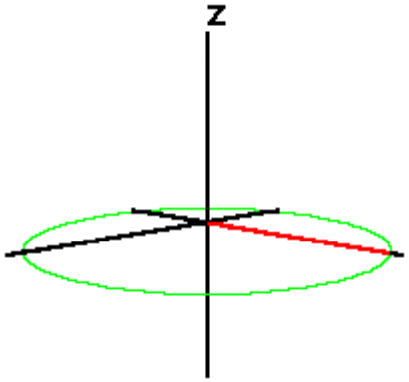
Rotating Frame of Reference…

It is convenient to define a rotating frame of reference which **rotates about the Z axis at the Larmor frequency**. We distinguish this rotating coordinate system from the laboratory system by primes on the X and Y axes, **X'Y'**.

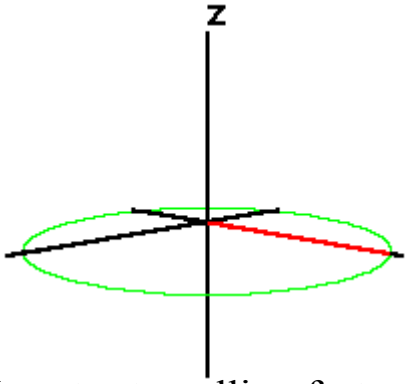




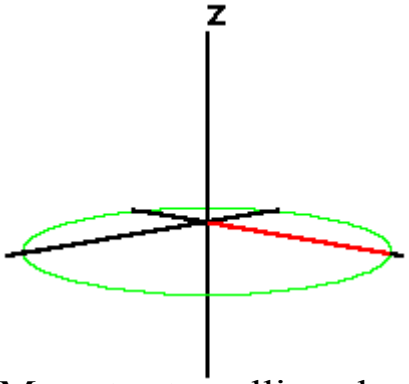
Longitudinal M: same as before



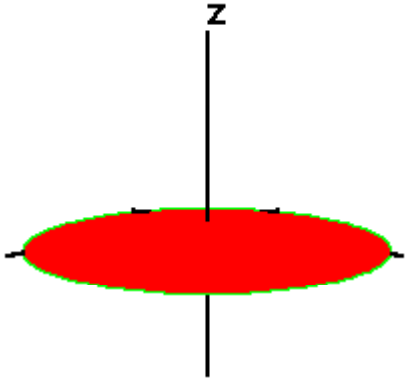
Transverse M: seems stationery



M vector travelling faster than Larmor

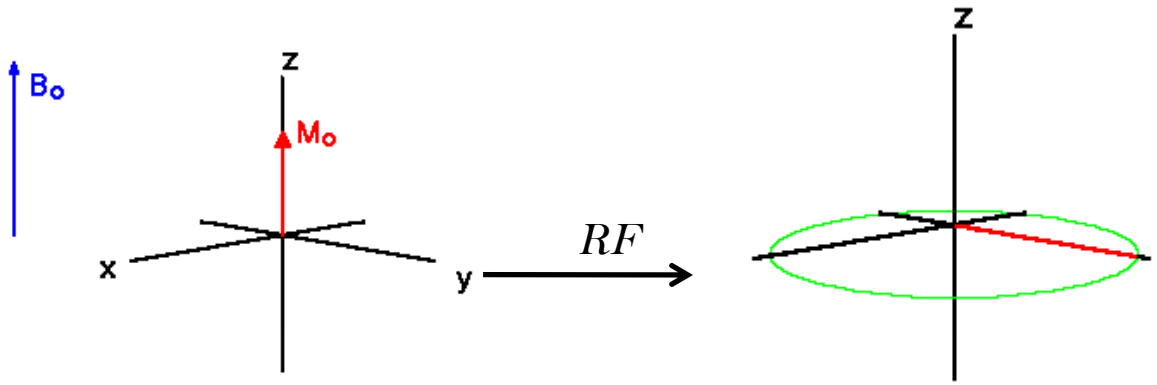


M vector travelling slower than Larmor



dephased

The 90-FID Sequence



The magnitude of the vector decays with time constant T_2^*

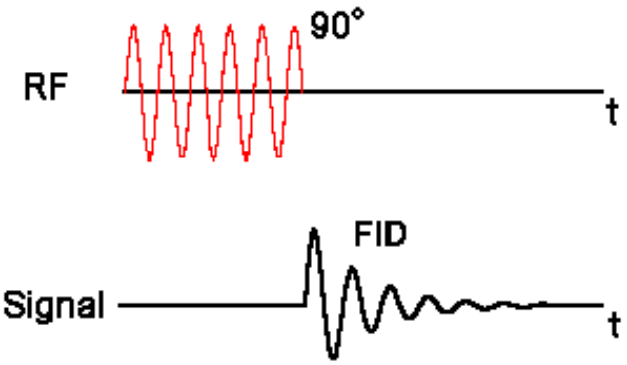
When this sequence is repeated, (when signal-to-noise improvement is needed, the amplitude of the signal after being Fourier transformed (S) will depend on T_1 and the time between repetitions, called the repetition time (TR), of the sequence. In the signal equation below, *k* is a proportionality constant and ρ is the density of spins in the sample.

$$S = k\,\rho\,(1 - e^{-TR/T1})$$

Available signal

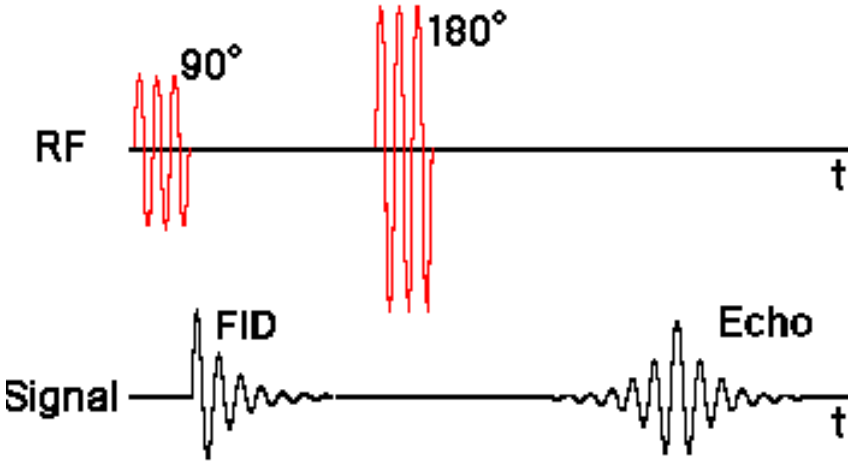
All spins

Spins returned to Z

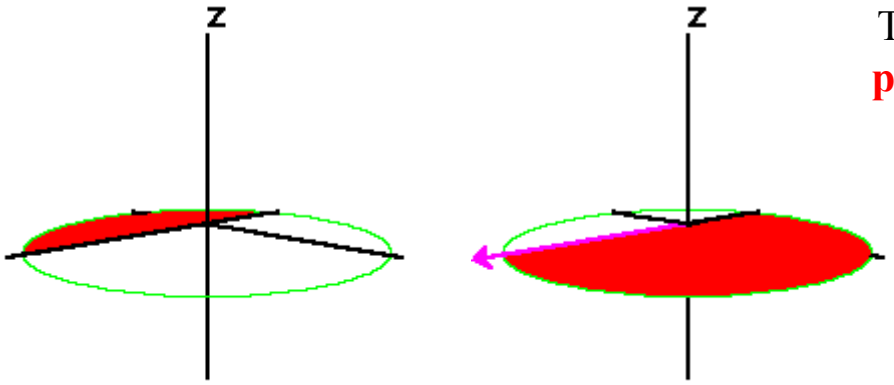


Detector on X' or Y', or X' and Y'…
NOT on Z

The Spin-Echo Sequence



1) A 90° pulse is first applied to the spin system that flips M to X'Y'….dephasing begins (like before).
2) At some point after the 90° pulse, a **SECOND 180° pulse** hits the sample. This pulse rotates the magnetization by 180° about the X' axis



The 180° pulse causes the magnetization to at least **partially rephase** and to produce a signal called an **echo**

$$S = k\ \rho\ (1 - e^{-TR/T1})\ e^{-TE/T2}$$

TR: repetition time
TE: Echo time

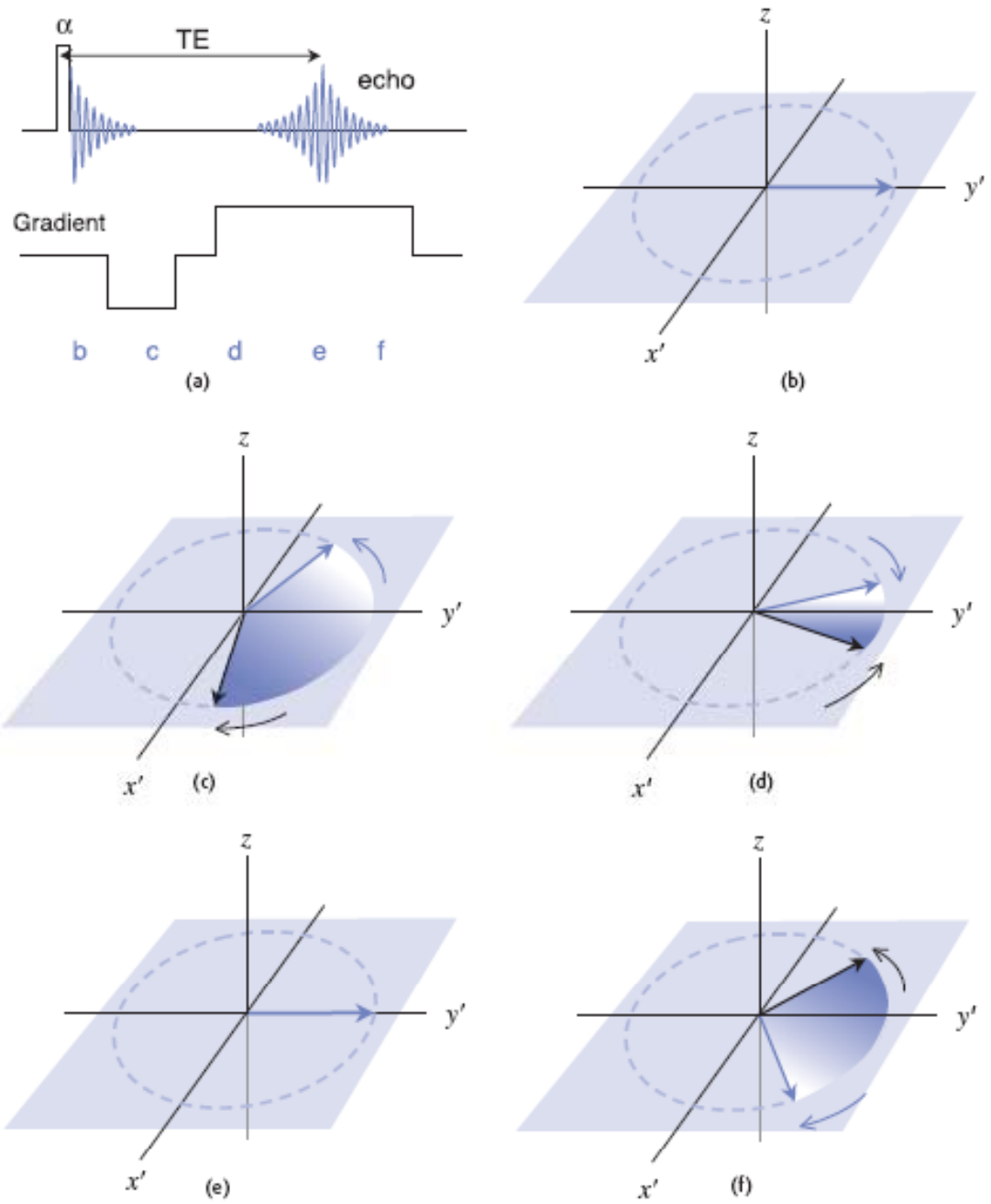
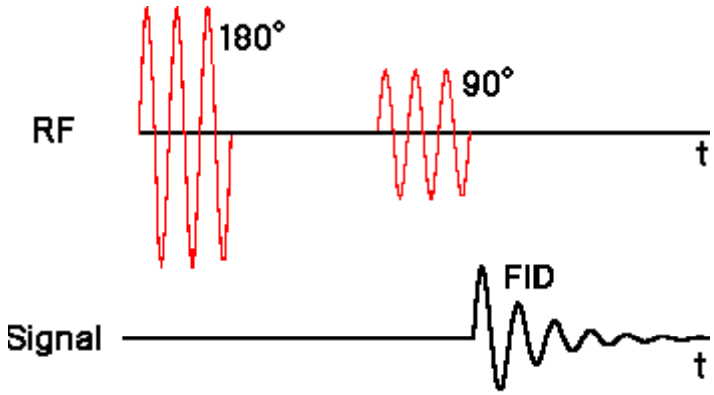


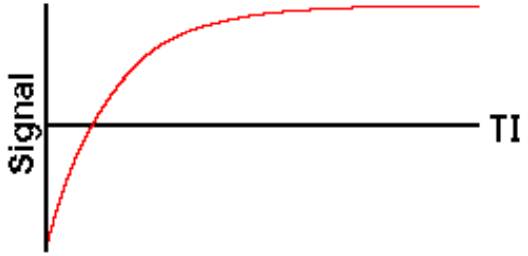
Figure 8.9 (a) Simple gradient-echo sequence. (b) Spins initially along the y axis are rapidly dephased by the negative lobe (c). When the gradient is switched positive (d), the spins begin to rephase, forming an echo (e). If the gradient is left on (f) dephasing will occur again.

The Inversion Recovery Sequence



1) a 180° pulse is first applied. This rotates the net magnetization down to the -Z axis.
2) Before it reaches equilibrium, a 90° pulse is applied which rotates the longitudinal magnetization into the XY plane
3) Once magnetization is present in the XY plane it rotates about the Z axis and diphases giving a FID.

$$S = k\ \rho\ (1 - 2e^{-TI/T1})$$



When an inversion recovery sequence is repeated **every TR seconds**, for signal averaging or imaging purposes, the signal equation becomes:

$$S = k\ (1 - 2e^{-TI/T1} + e^{-TR/T1})$$

…chemical Shift…eh???

When you place an atom in a magnetic field, its electrons will "feel" it as well…not only the nucleus….e^- form a 2ndary magnetic field "protecting" the nucleus….so the nucleus feels a somewhat smaller field than the external!

$$B_{eff} = B_o (1-s)$$

The opposing field (and the effective field) at each different nucleus will vary, according to its nature and its bonding in the molecule… This is the **chemical shift phenomenon.**

The chemical shift of a nucleus is **the difference between the resonance frequency of the nucleus and a standard, relative to the standard.** This quantity is reported in **ppm** and given the symbol delta, δ.

$$\delta = (\nu - \nu_{REF}) \times 10^6 / \nu_{REF}$$

Questions and Problems…again…!

1) From the ^1H NMR perspective, the human body is composed primarily of fat hydrogens ($-CH_2-$) and water hydrogens (H_2O). The resonance frequency difference between the NMR signal from these two types of hydrogens is approximately 220 Hz on a 1.5 Tesla imager. What is the chemical shift difference?

$g(^1H)=42.58$ MHz/T

2) The hydrogen T_1, T_2 and spin density values for common brain tissues are listed in the following table:

Tissue	T_1 (s)	T_2 (ms)	r*
CSF	0.8 - 20	110 - 2000	70-230
White	0.76 - 1.08	61-100	70-90
Gray	1.09 - 2.15	61 - 109	85 - 125
Meninges	0.5 - 2.2	50 - 165	5 - 44
Muscle	0.95 - 1.82	20 - 67	45 - 90
Adipose	0.2 - 0.75	53 - 94	50 - 100

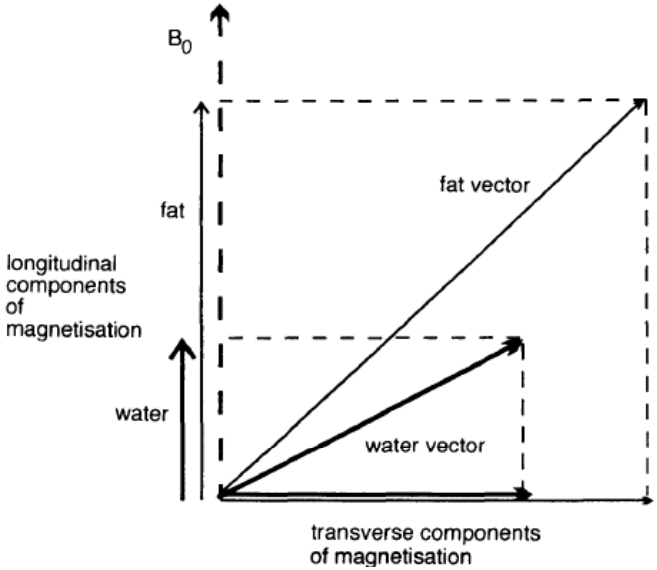
At what TI value is the signal from fat approximately equal to zero in an inversion recovery sequence?

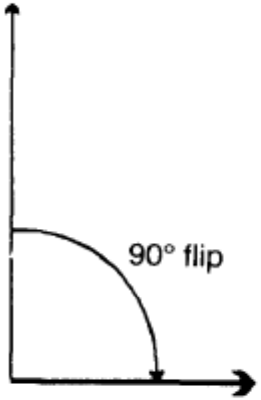
3) When using a 90-FID pulse sequence and a sample containing all the tissues in question number two, what TR value would guarantee at least 98% of the signal from all the tissues?

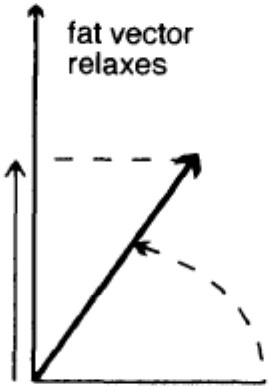
4) spin-echo pulse sequence

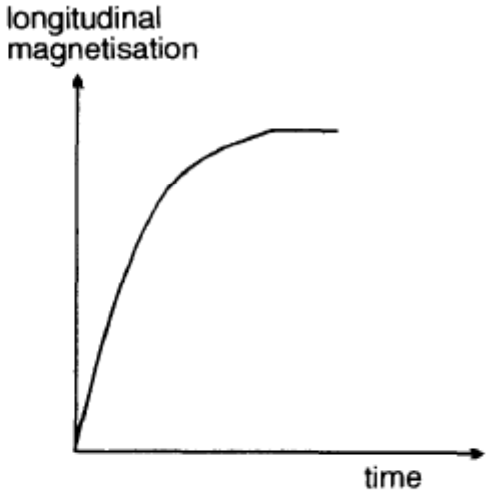
5) You are using a and the adipose tissue sample in question number two. If the minimum TE value you can obtain is 20 ms, how much more signal could you obtain with a 90-FID sequence?

T_1 in fat and water

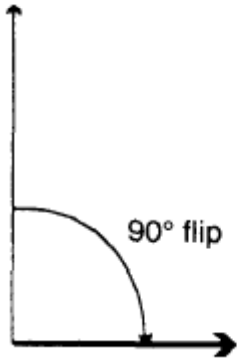


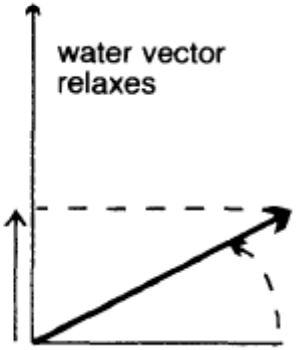


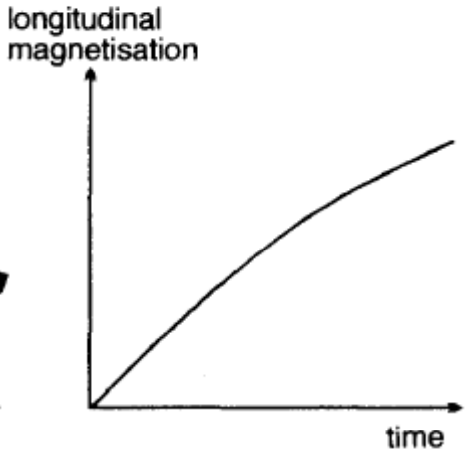




fat regains longitudinal magnetisation rapidly

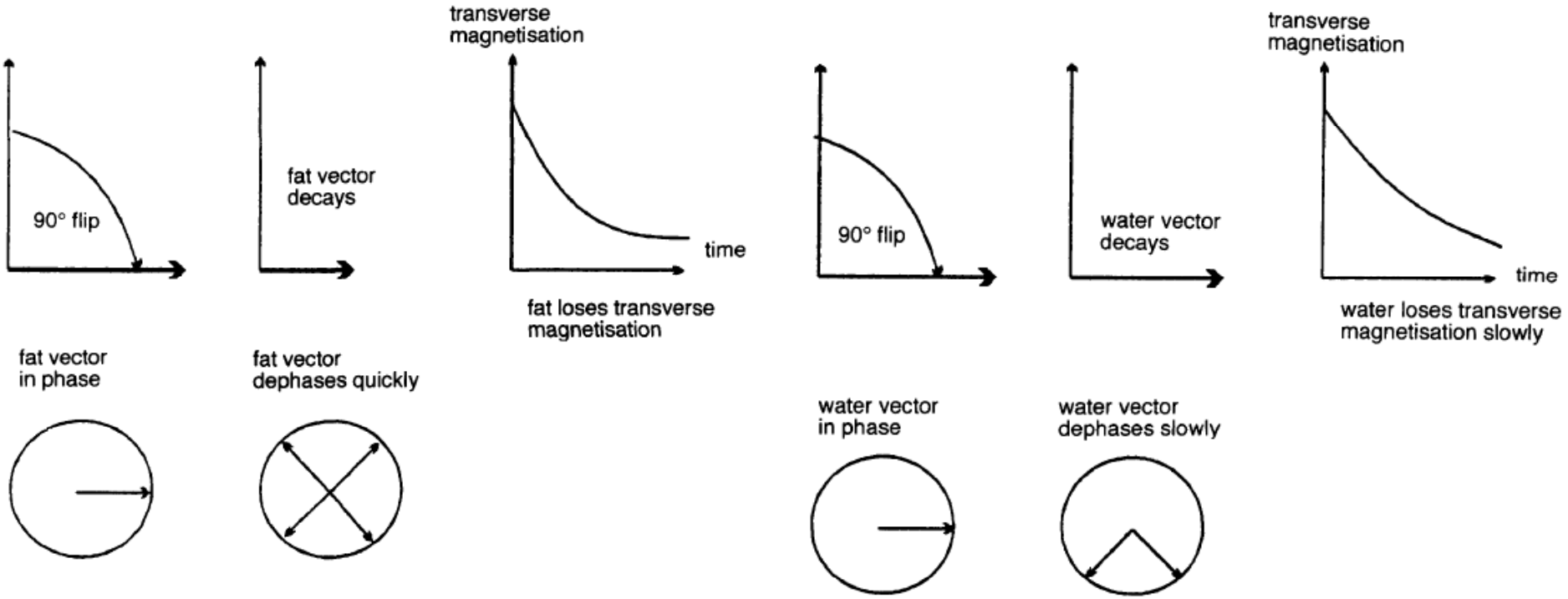






water regains longitudinal magnetisation slowly

T_2 in fat and water



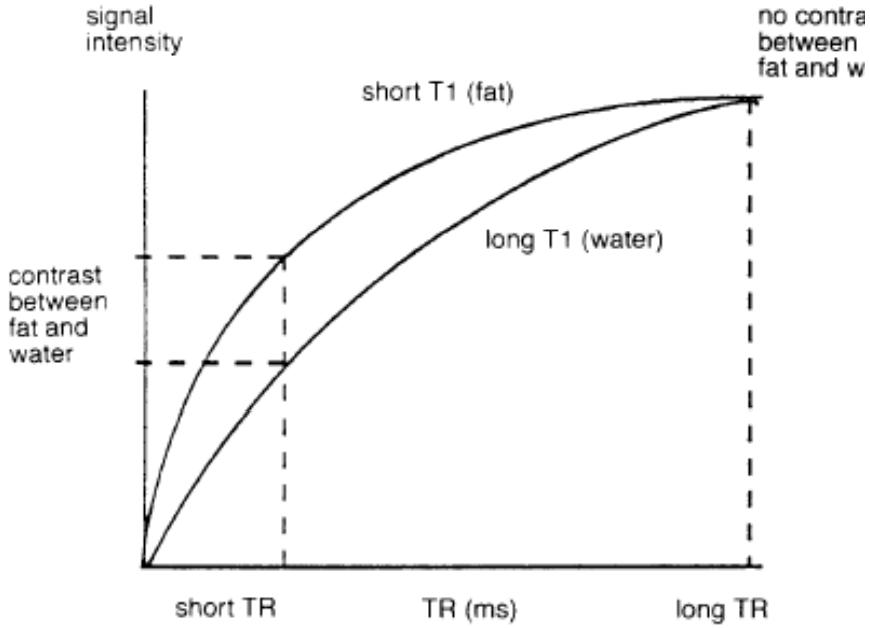
As there is more longitudinal magnetisation in fat before the RF pulse, there is more transverse magnetisation in fat after the RF pulse. Fat therefore has a high signal and appears bright on a T1 contrast image. As there is less longitudinal magnetisation in water before the RF pulse, there is less transverse magnetisation in water after the RF pulse. Water therefore has a low signal and appears dark on a T1 contrast image. Such images are called T1 weighted images.

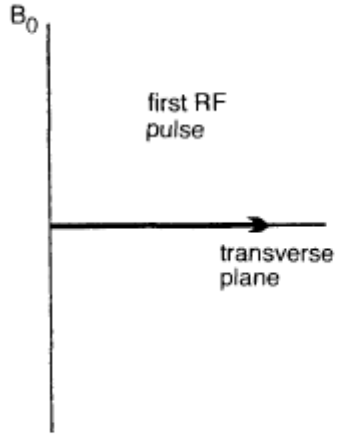
The T2 time of fat is shorter than that of water, therefore the transverse component of magnetisation of fat decays faster. The magnitude of transverse magnetisation in water is large. Water has a high signal and appears bright on a T2 contrast image. However, the magnitude of transverse magnetisation in fat is small. Fat therefore has a low signal, and appears dark on a T2 contrast image (Fig. 2.7). Such images are called T2 weighted images.

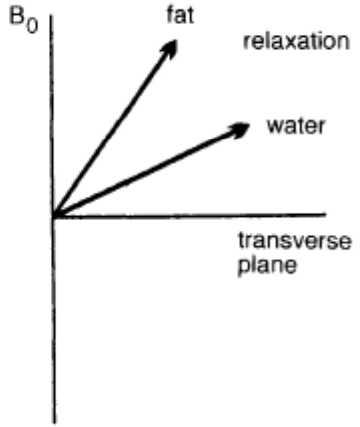
T_1 weighted images

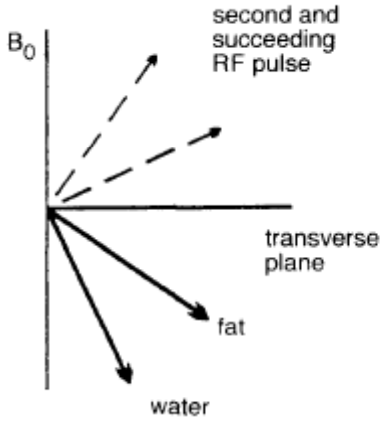
- TR controls the amount of T1 weighting.
- For T1 weighting the TR must be short.

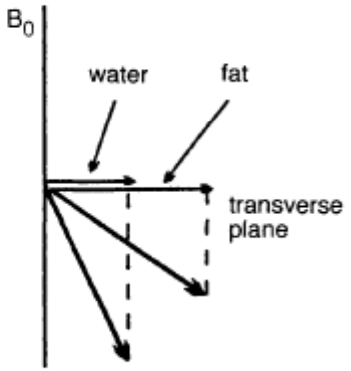
$$S = k\ \rho\ (1 - e^{-TR/T1})\ e^{-TE/T2}$$







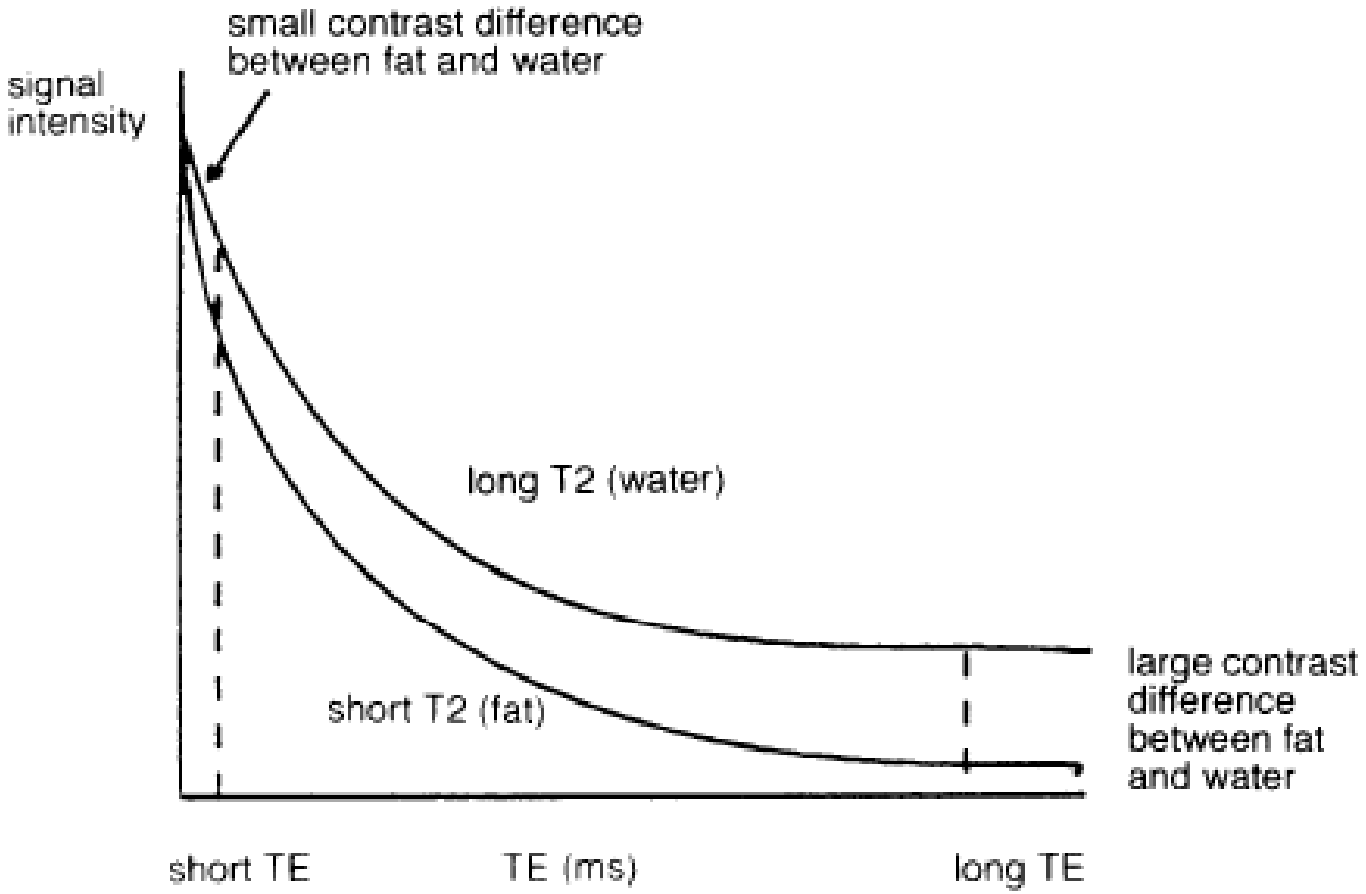




T_2 weighted images

- TE controls the amount of T2 weighting.
- For T2 weighting the TE must be long.

$$S = k\ \rho\ (1 - e^{-TR/T1})\ e^{-TE/T2}$$



Have to remember that:

- Fat has a short T1 and T2 time.
- Water has a long T1 and T2 time.
- To produce high signal, there must be a large component of magnetisation in the transverse plane to induce a large signal in the coil.
- To produce a low signal, there must be a small component of magnetisation in the transverse plane to induce a small signal in the coil.
- T1 weighted images are characterised by bright fat and dark water.
- T2 weighted images are characterised by bright water and dark fat.
- Proton density weighted images are characterised by:
  areas with high proton density are bright,
  areas with low proton density are dark.

PD (proton density ….how many protons are we measuring)

T_1

T_2

TR (affects T_1)

TE (affects T_2)

Table 3.1 Choice of TR and TE for conventional spin echo sequences

TR	TE	
	Short (less than 40 ms)	Long (more than 75 ms)
Short (less than 750 ms)	T_1-weighted	Not useful
Long (more than 1500 ms)	PD-weighted	T_2-weighted

…enough with NMR….let's talk inorganic chemistry now….

Paramagnetic Complexes in MRI…

Milestones…

1) Remember Bloch??? (the guy who invented NMR in 1946…)

He used $Fe(NO_3)_3$ to speed up longitudinal relaxation $1/T_1$ (shorten T_1)

2) PRE: Proton Relaxation Enhancement

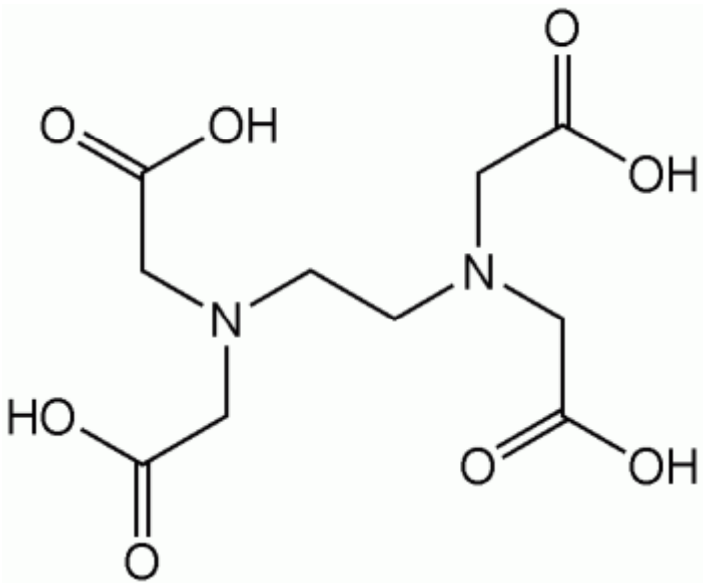
Eisinger, Shulman and Blunberg showed that when a paramagnetic metal binds to a molecule (DNA in their case) it speeds up H relaxation…so that it gives NO SIGNAL…and the contrast is better!

3) Laterbur in 1973…did the same with dog heart coronal tissues. Laterbur, Mendoca-Dias, Rudin showed the efficiency of paramagnetic metal ions to improve the diff. between healthy and "non-healthy" tissues…

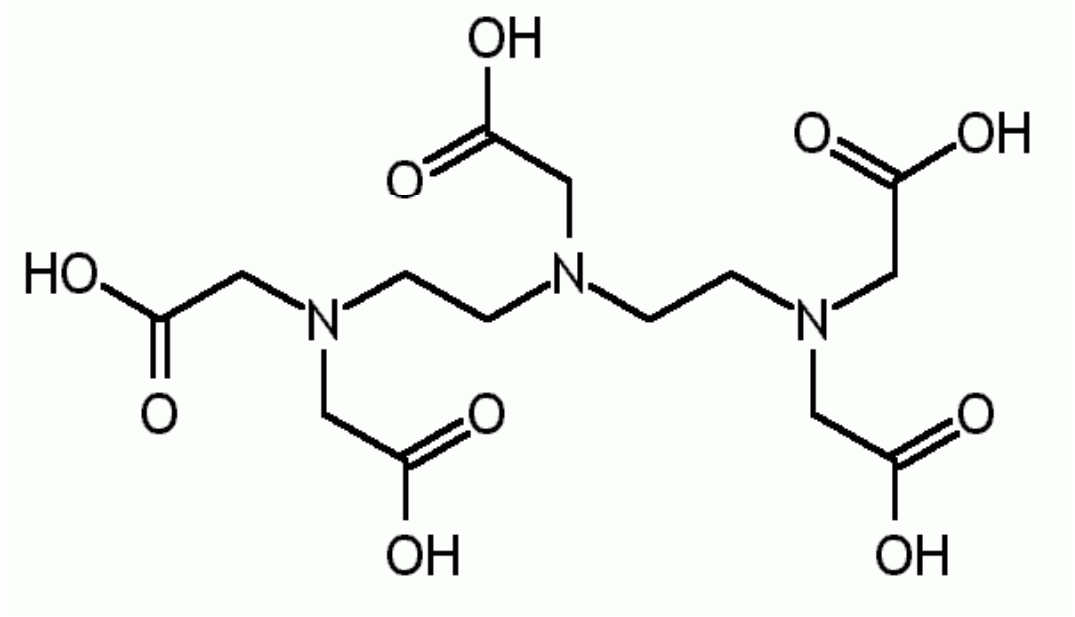
The paramagnetic metal improves the contrast between tissues..by "darkening" or "whitening"one type of issues…either the "good" ones or the "bad" ones

4) Young at al. in 1977…performed similar experiments to human patients!!!
They used $FeCl_3$ (aq.) (orally) as a means to "see" gastrointestinal areas!!!

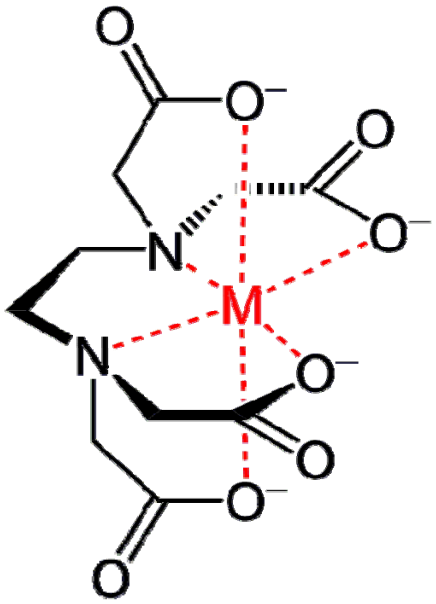
5) Carr et al. started using Gd(III) compounds…
$[Gd(DTPA)(H_2O)]^{2-}$ (1981). In use since 1988…



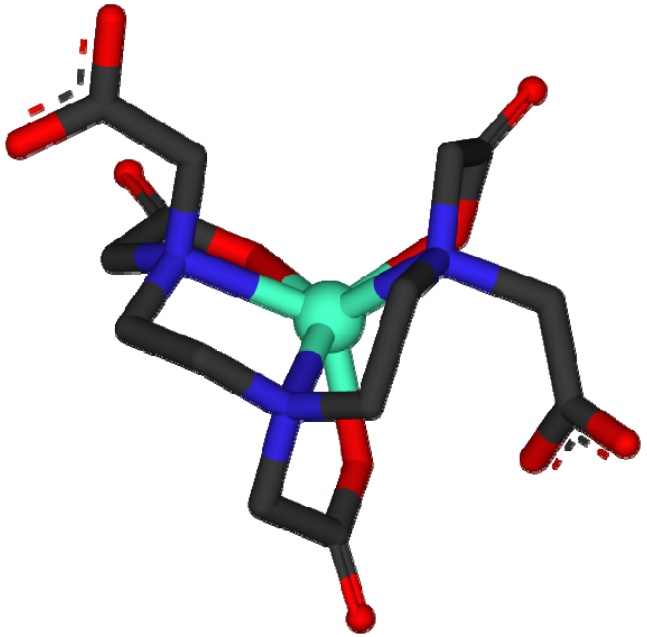
EDTA:
Ethylene Diamine Tetraacetic Acid



DTPA:
DiethyleneTriamine Pentaacetic Acid



M-EDTA chelate



"Gadopentetic acid" Gd-DPTA…
Magnevist Bayer Pharm.

It is usually injected intravenously to patients with brain tumors.

It provides "information" for intercranial lesions and for damaged blood vessels.

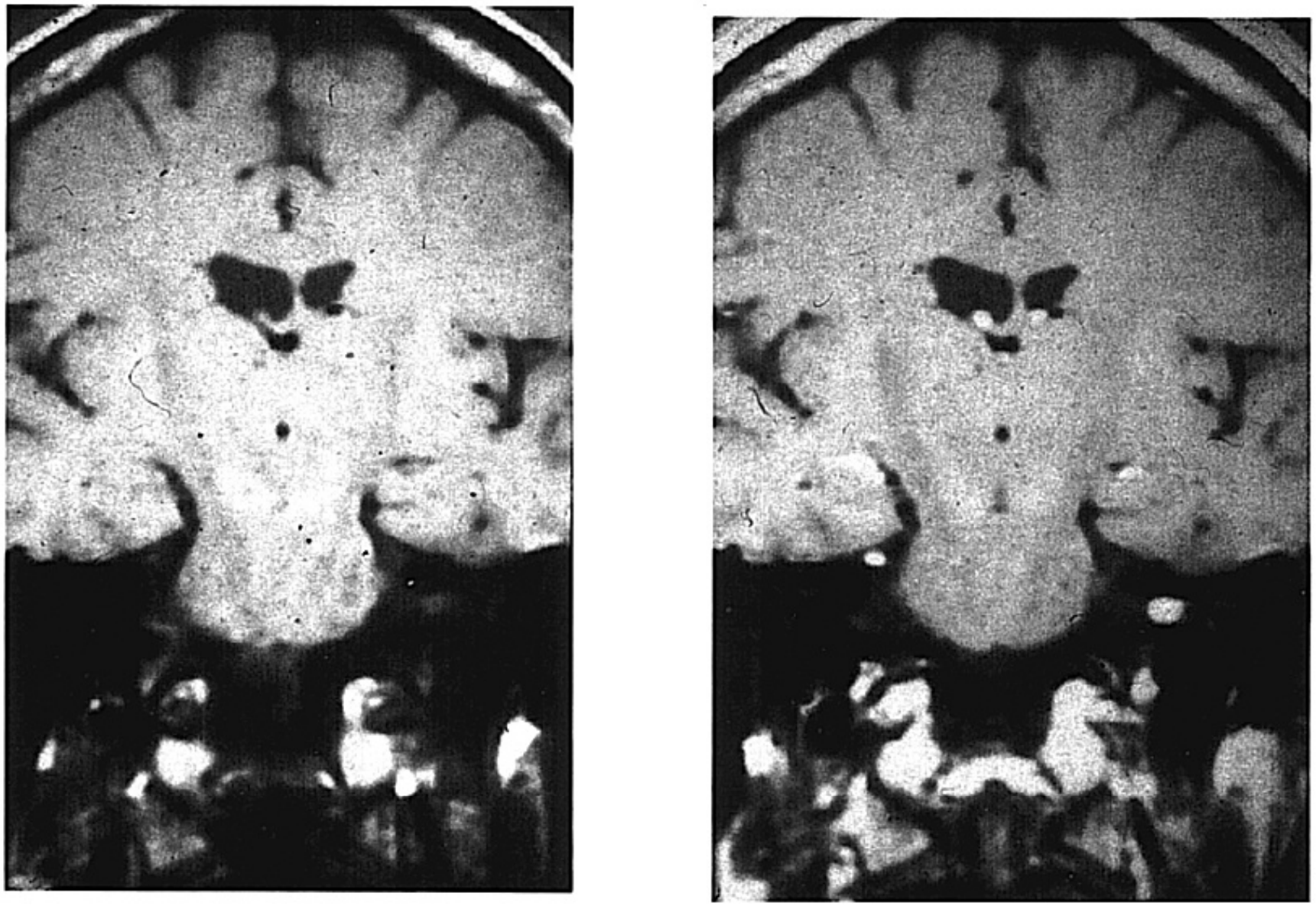


Fig. 11.4 Coronal T1 weighted images of the head pre- and post-gadolinium injection. On the enhanced image (right) an area within the internal auditory meatus has enhanced. This indicates an acoustic neuroma. There is also a tiny enhancing lesion on the fifth cranial nerve.

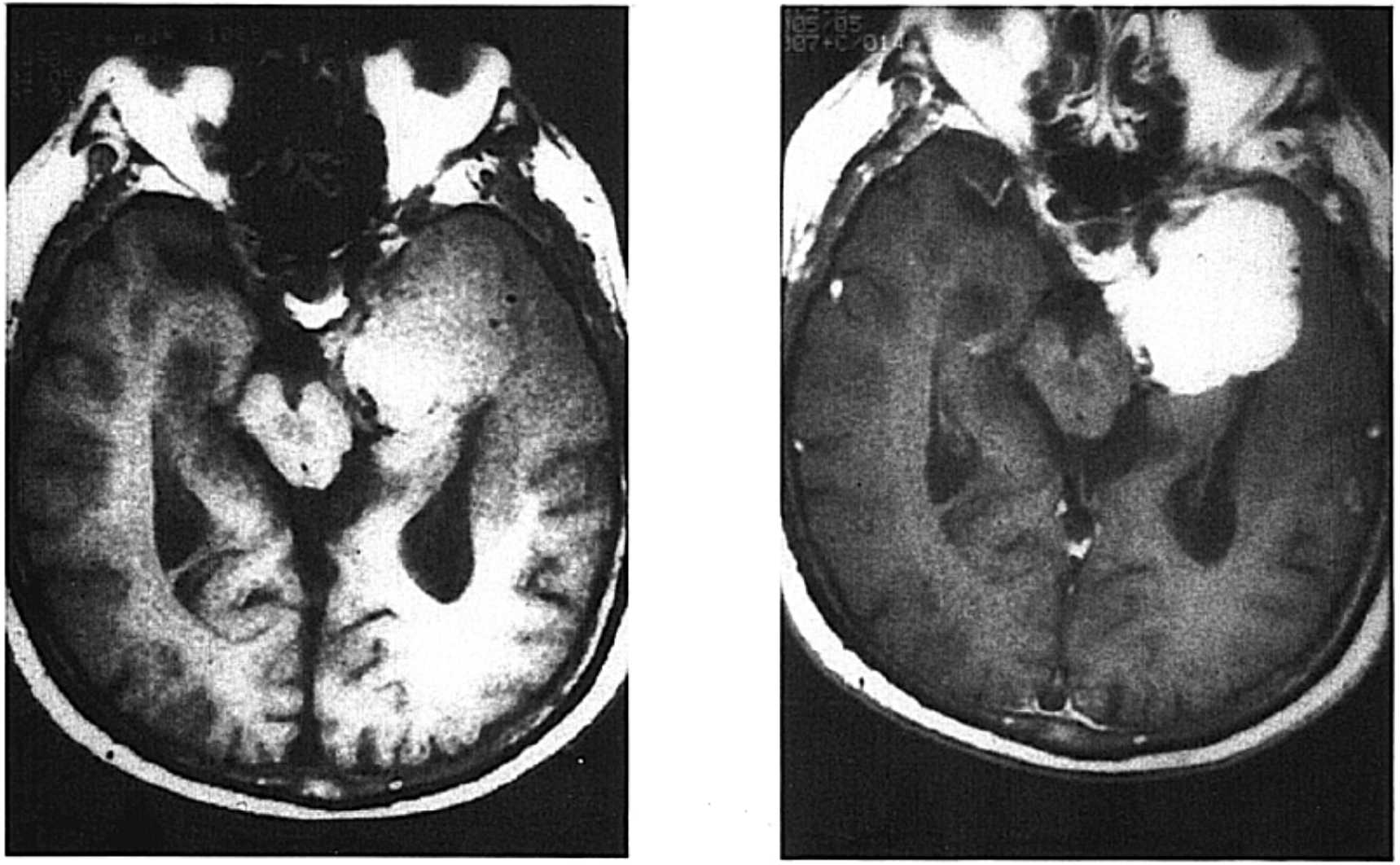


Fig. 11.5 Axial T1 weighted images of the brain pre- and post-gadolinium injection On the enhanced image (right) enhancement of the peripheral temporal lobe is demonstrated. This indicates a meningioma.

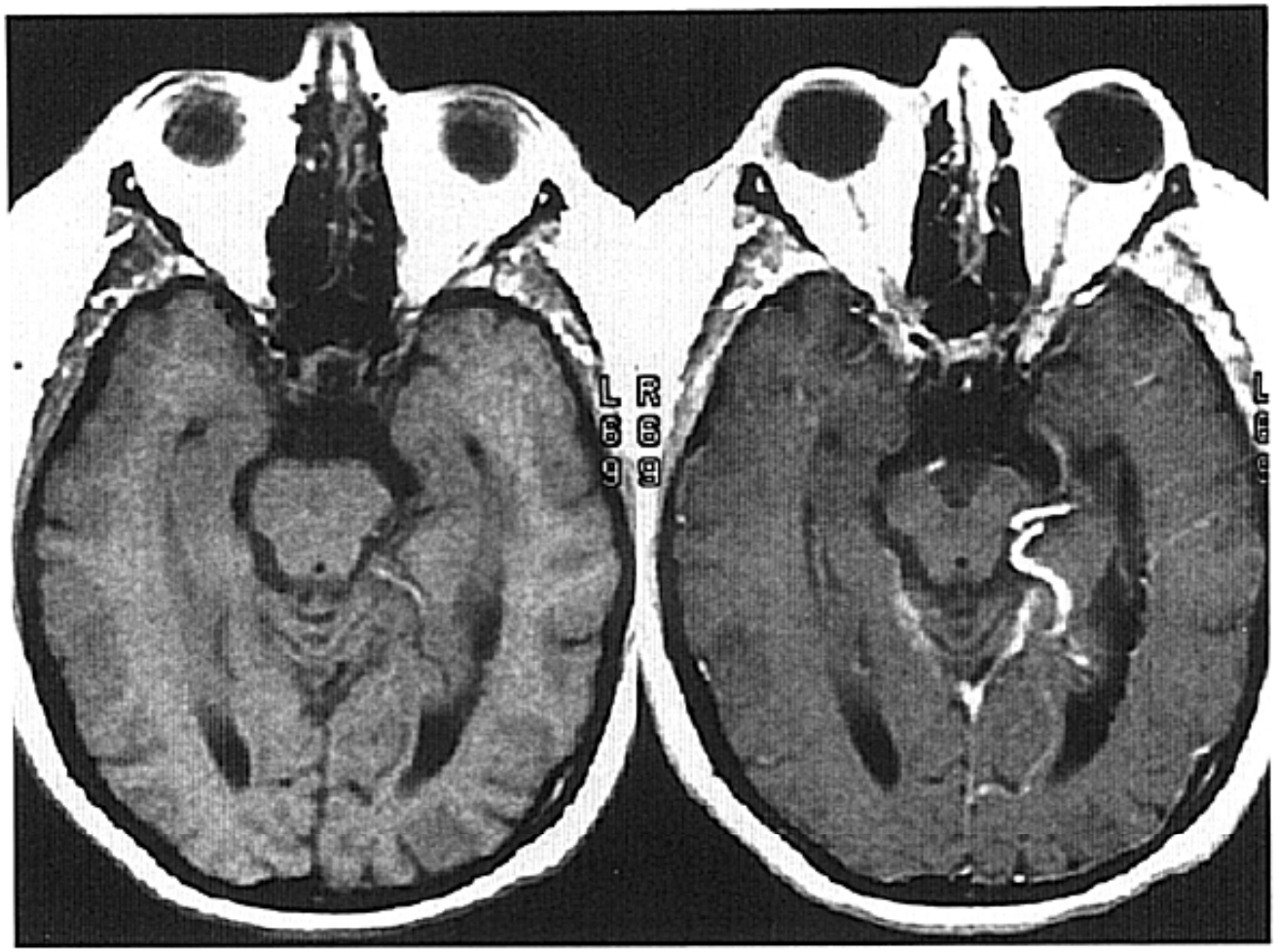


Fig. 11.6 These axial images of the brain were acquired before (left) and after (right) contrast enhancement. The slow flow in the arterio-venous malformation (AVM) demonstrates enhancement after contrast enhancement. The T2 and T2* weighted images for this case are given in Chapter 12 (Fig. 12.15) and can be compared.

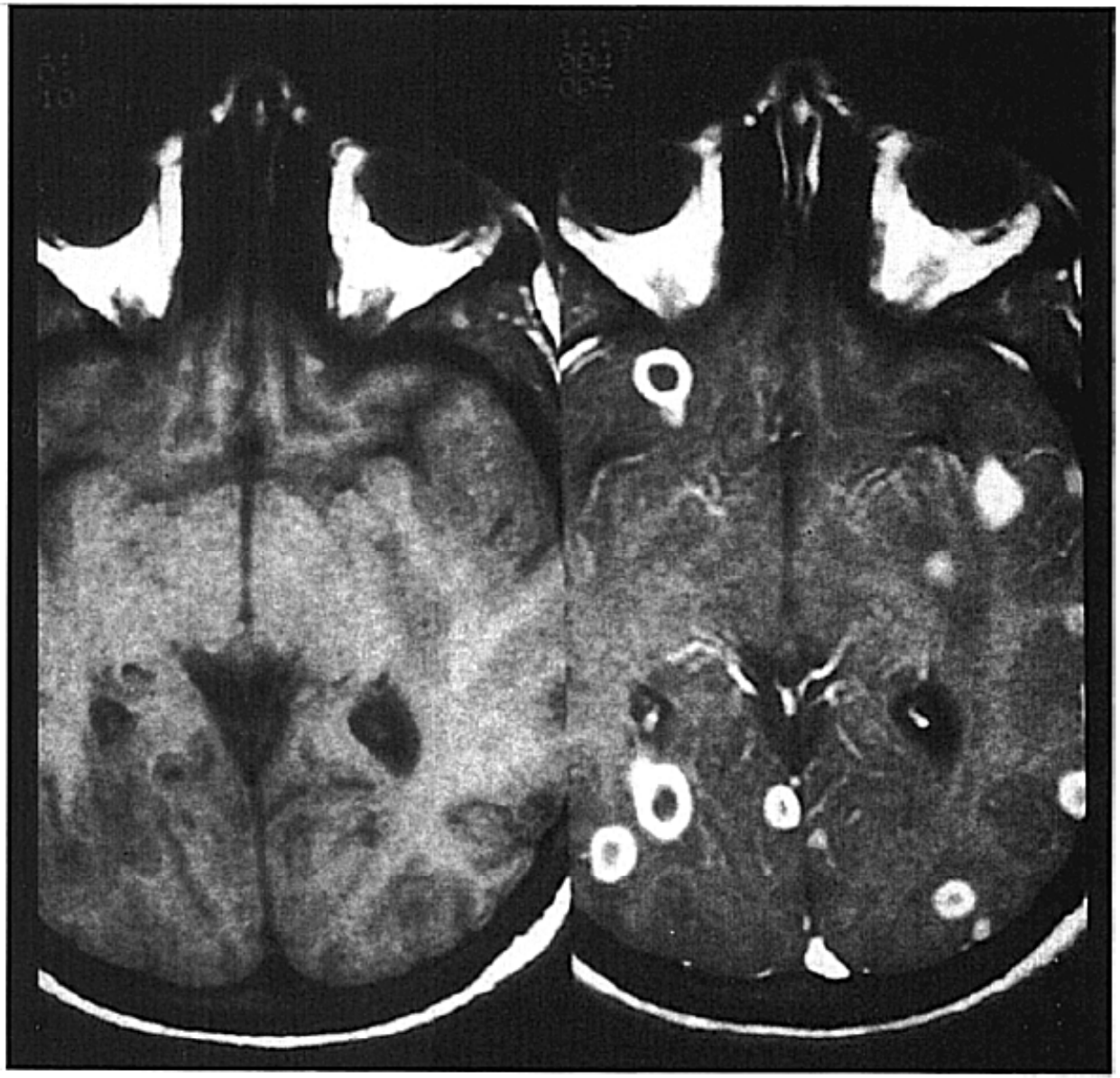


Fig. 11.7 Axial T1 weighted images pre- and post-injection of gadolinium. The ring enhancing lesions demonstrate toxoplasmosis in this 24-year-old male with AIDS.

…General Conditions for Paramagnetic Complexes in MRI….

1) **Biocompatible**, water soluble (no MeOH/EtOH/MeCN, etc…in human body) and stable…
2) **Relaxivity:** The efficiency with which the complex enhances the proton relaxation rates of water (i.e. *relaxivity*) must be sufficient to significantly increase the relaxation rates of the target tissue ….remember relaxation rate=$1/T_1$
3) The dose of the complex at which such alteration of tissue relaxation rates occurs must of course be **nontoxic**. As small as 10-20% increases in 1/T1 could be detected by NMR/MRI imaging.
4) **In vivo specific targetting…** the complex should localize for a period of time in compared to a non-targetted tissue.
5) **In vivo stability and Excreatability**…free metals toxic to humans…

Periodic Table of Elements

1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89 Ac	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Uun								

58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

Li Solid

Cs Liquid

Ar Gas

Lr Synthetic

Alkali metals

Alkali earth metals

Transition metals

Rare earth metals

Other metals

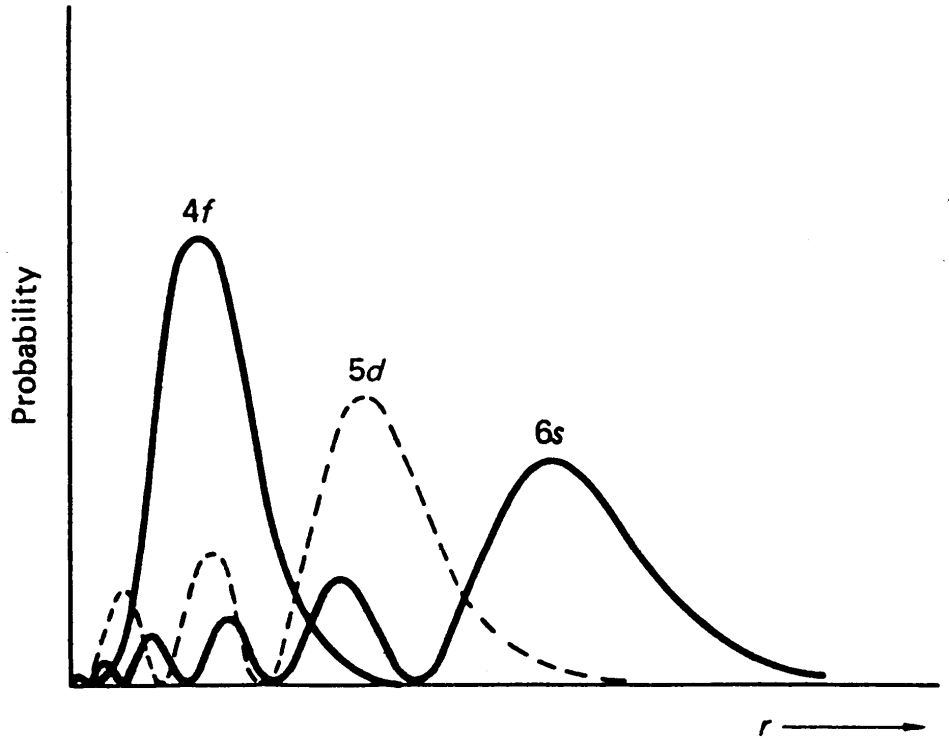
Noble Gases

Halogens

Other nonmetals

Lazy College Professors Never Produce Sufficiently Educated Graduates To Dramatically Help Executives Trim Yearly Losses.

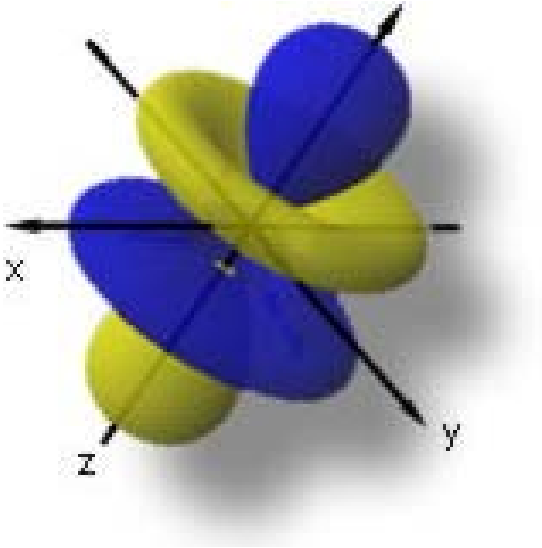
f orbitals



Το ακτινικό τμήμα των υδρογονοειδών κυματοσυναρτήσεων για τα *4f*, *5d* και *6s* τροχιακά του Ce

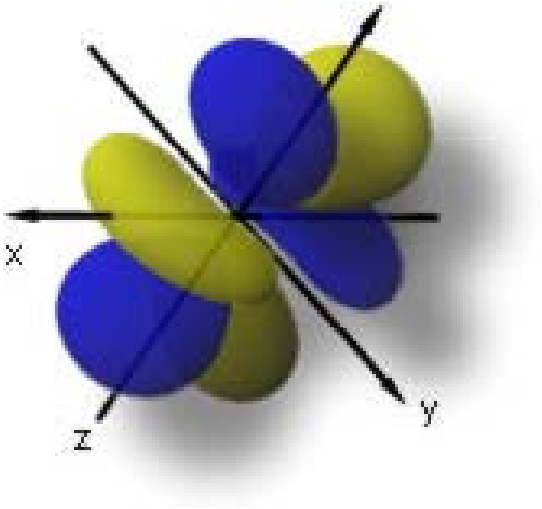
Cubic set: $f_x^3, f_y^3, f_z^3, f_{xyz}, f_{x(z^2-y^2)}, f_{y(z^2-x^2)}, f_{z(x^2-y^2)}$

General set: $f_z^3, f_{xz^2}, f_{yz^2}, f_{xyz}, f_{z(x^2-y^2)}, f_{x(x^2-3y^2)}, f_{y(3x^2-y^2)}$



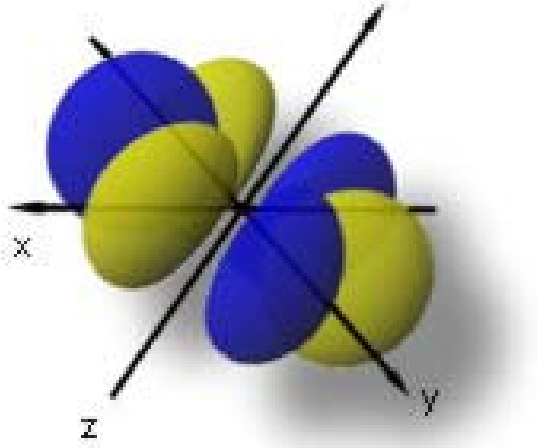
f_z^3

f_x^3 and f_y^3 orbitals have the same shape but lie on x and y axis, respectively



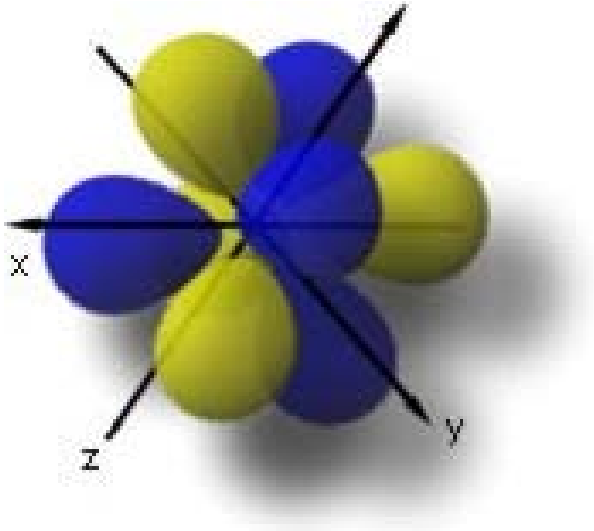
f_{xz}^2

f_{yz}^2 same shape, rotated by 90^o around z



$f_{x(x^2 - 3y^2)}$

$f_{y(3x^2 - y^2)}$ same shape, but 90° left turn around z.



f_{xyz}

$f_{x(z^2-y^2)}$, $f_{y(z^2-x^2)}$ and $f_{z(x^2-y^2)}$ come from 45° rotation around x, y and z respectively.

Lanthanide Contraction

Element	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Atomic electronic config	$4f^1 5d^1 6s^2$	$4f^3 6s^2$	$4f^4 6s^2$	$4f^5 6s^2$	$4f^6 6s^2$	$4f^7 6s^2$	$4f^7 5d^1 6s^2$	$4f^9 6s^2$	$4f^{10} 6s^2$	$4f^{11} 6s^2$	$4f^{12} 6s^2$	$4f^{13} 6s^2$	$4f^{14} 6s^2$	$4f^{14} 5d^1 6s^2$
Ln^{3+} electron config	$4f^1$	$4f^2$	$4f^3$	$4f^4$	$4f^5$	$4f^6$	$4f^7$	$4f^8$	$4f^9$	$4f^{10}$	$4f^{11}$	$4f^{12}$	$4f^{13}$	$4f^{14}$
Ln^{3+} radius(pm) -6 coord.	102	99	98.3	97	95.8	94.7	93.8	92.3	91.2	90.1	89	88	86.8	86.1

…Why Ln complexes in MRI ?….

General Characteristics of Ln

1) Similar properties throughout the Ln row

2) Most common oxidation state: +3

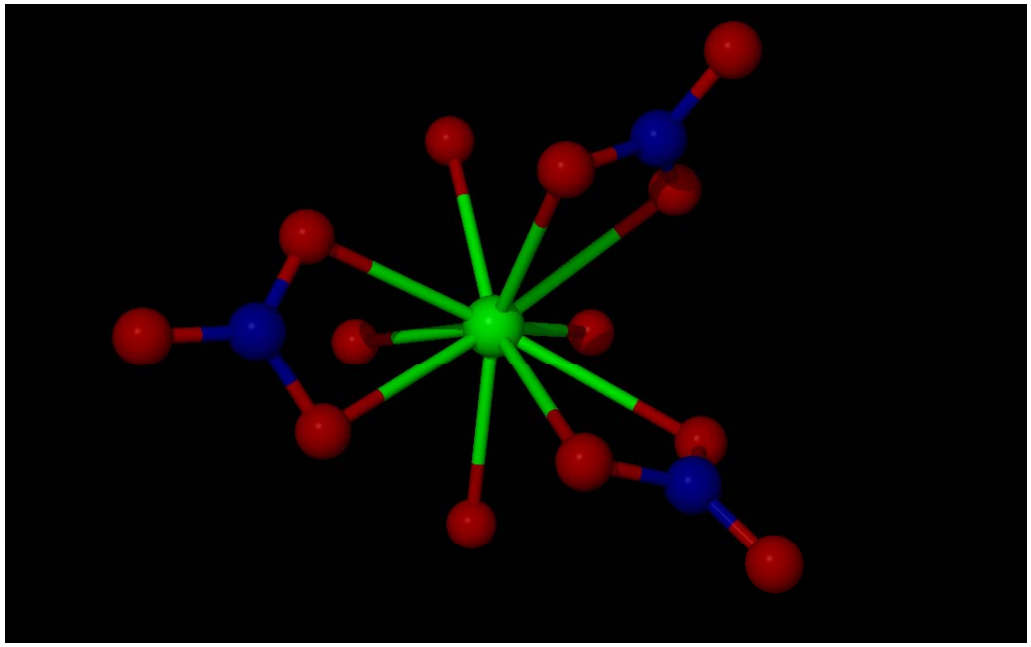
3) Coordination numbers >6. Most common ones:8-9

4) Coordination polyhedra mainly affected by steric factors, not electronic.

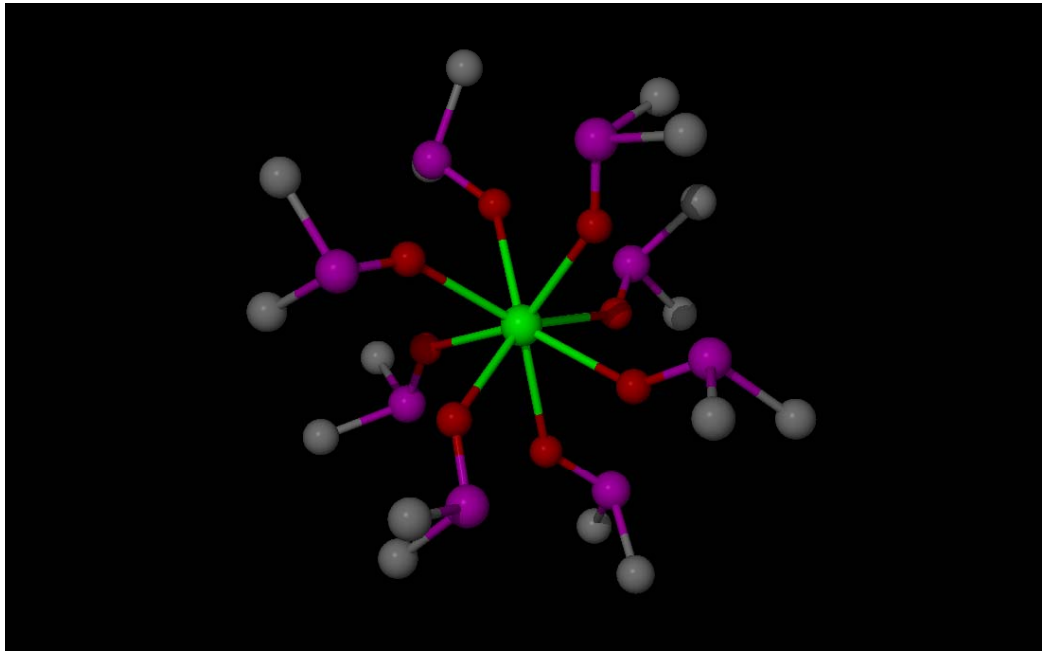
5) They prefer "hard donors", such as O, F, …

6) Their magnetic properties are generally not affected by their environment

7) They can exchange ligands very rapidly…



$[Pr(NO_3)_3(H_2O)_4]\cdot H_2O$



$[Ln(DMSO)_8(ClO_4)_3]$

Theory and mechanisms…Relaxivity

So, what happens when we get the Ln complex in the tissue? ***2*** main possibilities….

Inner Sphere Mechanism

Remember property no. 7 ???...”exchange ligands rapidly”…

Relaxation time of free water = 10^6 x relax. time of bound to Gd water…

Decrease of T_1 and/or T_2 means better signal…remember Spin-Echo sequence???

$$S = k\ \rho\ (1 - e^{-TR/T1})\ e^{-TE/T2}$$ Spin-Echo Sequence

$$\Delta T_1^{-1} = R_1 [p]$$
$$\Delta T_2^{-1} = R_2 [p]$$

R: relaxivity
[p]: paramagnetic metal

Best Signal when $R_2/R_1 = 1$

Solomon, Bloembergen Equations

$$(1/T_i)_{obsd} = (1/T_i)_d + (1/T_i)_p \quad i = 1, 2$$

$T_{i\,obs}$: observed T_i
$T_{i\,d}$: T_i without the metal
$T_{i\,p}$: Additional paramagnetic contribution

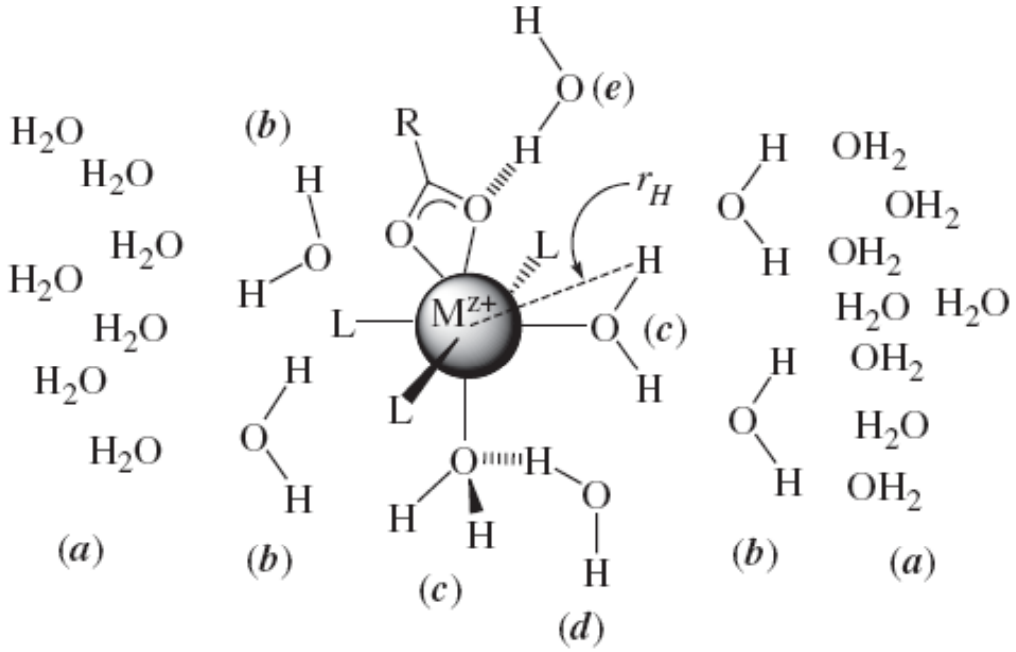
$$(1/T_i)_p = (1/T_i)_{inner\ sphere} + (1/T_i)_{outer\ sphere} \quad i = 1, 2$$

$$\left[\frac{1}{T_1}\right]\text{(inner sphere)} = \frac{P_M q}{T_{1M} + \tau_M}$$

P_M: mole fraction of metal
q: number of H_2Os bound per metal
T_{1M}: relaxation time of bound water
τ_M: residence lifetime of bound water

$$\frac{1}{T_{1M}} = \frac{2}{15}\frac{\gamma_I^2 g^2 S(S+1)\beta^2}{r^6}\left[\frac{7\tau_c}{(1+\omega_S^2\tau_c^2)} + \frac{3\tau_c}{(1+\omega_I^2\tau_c^2)}\right] + \frac{2}{3}S(S+1)\left(\frac{A}{\hbar}\right)^2\left[\frac{\tau_e}{1+\omega_S^2\tau_c^2}\right]$$

γ_I: H gyromagnetic ratio
***g*: electon g-factor**
***S*: total spin of the metal**
β: bohr magneton
***r*: proton – metal distance**
ω_S, ω_I: electronic, proton Larmor freq.
$A/\hbar$: electron-nuclear hyperfine coupl.
r_c: correlation time…rotational movement, tumbling, etc…



A schematic representation of the different types of water molecule around a metal ion in a complex $[ML_3(RCO_2)(H_2O)_2]^{z+}$ in aqueous media (a) bulk water; (b) 'outer sphere' water; (c) 'inner sphere' water. The distance rH is from the metal ion to a proton in an inner sphere water molecule; (d) an 'outer sphere' water molecule hydrogen bonded to an inner sphere water molecule so that one proton becomes essentially inner sphere; (e) an 'outer sphere' water molecule hydrogen bonded to an inner sphere ligand carboxylate oxygen so that one proton becomes essentially inner sphere

$$\frac{1}{T_{1M}} = \frac{2}{15}\frac{\gamma_I^2 g^2 S(S+1)\beta^2}{r^6}\left[\frac{7\tau_c}{(1+\omega_S^2\tau_c^2)} + \frac{3\tau_c}{(1+\omega_I^2\tau_c^2)}\right] + \frac{2}{3}S(S+1)\left(\frac{A}{\hbar}\right)^2\left[\frac{\tau_e}{1+\omega_S^2\tau_c^2}\right]$$

correlation time

$$\frac{1}{\tau_c} = \frac{1}{T_{1e}} + \frac{1}{\tau_M} + \frac{1}{\tau_R}$$ dipolar relaxation mechanism

$$\frac{1}{\tau_e} = \frac{1}{T_{1e}} + \frac{1}{\tau_M}$$ scalar relaxation mechanism

T_{1e}: the longitudinal electron spin relaxation time

τ_M: residence lifetime of bound water

τ_R: the rotational tumbling time of the entire metal-water unit

$$\frac{1}{T_{1e}} = B\left[\frac{\tau_V}{1+\omega_S^2\tau_V^2} + \frac{4\tau_V}{1+4\omega_S^2\tau_V^2}\right]$$

When $S > 1/2$ we have to consider ZFS effects as well…

ZFS

…Things we should remember …:

1) Relaxation Times decrease a lot when H_2O binds to metal

2) $\Delta T_1^{-1} = R_1\,[p]$

3) $\Delta T_2^{-1} = R_2\,[p]$

4) Best Signal for $R_2/R_1 = 1$

5) Relaxivity depends on dipole-dipole interactions between proton spin and electron spin… either in inner or outer sphere

6) Correlation times (r_c) depend on the size of the metal containing compound…the bigger the size, the smaller T_1 and T_2 become due to tumbling and rotational movement !!!!

Outer Sphere Mechanism: far too complicated…

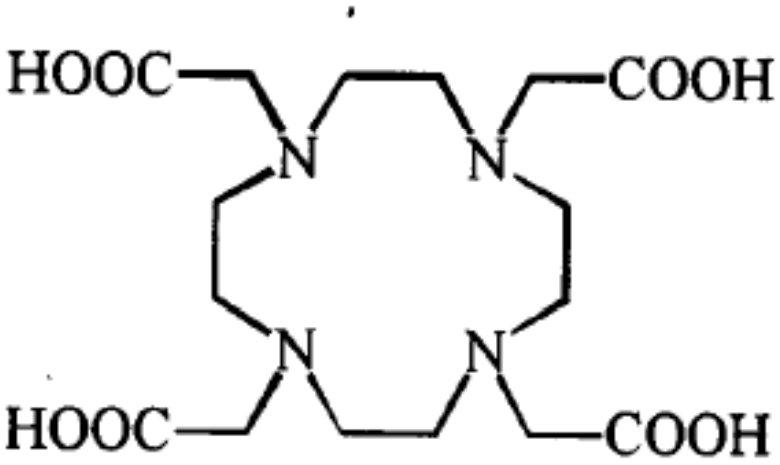
$$\left[\frac{1}{T_1}\right]_{\text{outer sphere}} = \frac{C\pi N_S \gamma_I^2 \gamma_S^2 \hbar^2 S(S+1)}{d^3 \tau_D}[7I(\omega_S, \tau_D, T_{1e}) + 3I(\omega_I, \tau_D, T_{1e})]$$

$$\tau_D = d^2/3(D_I + D_S)$$

C: numerical constant
Ns: the number of metals per cm^3
d: the distance of closest approach of the solvent molecule to the metal complex
r_D: the relative translational diffusion time
D_I, D_s : the diffusion coefficients of water and the metal complex

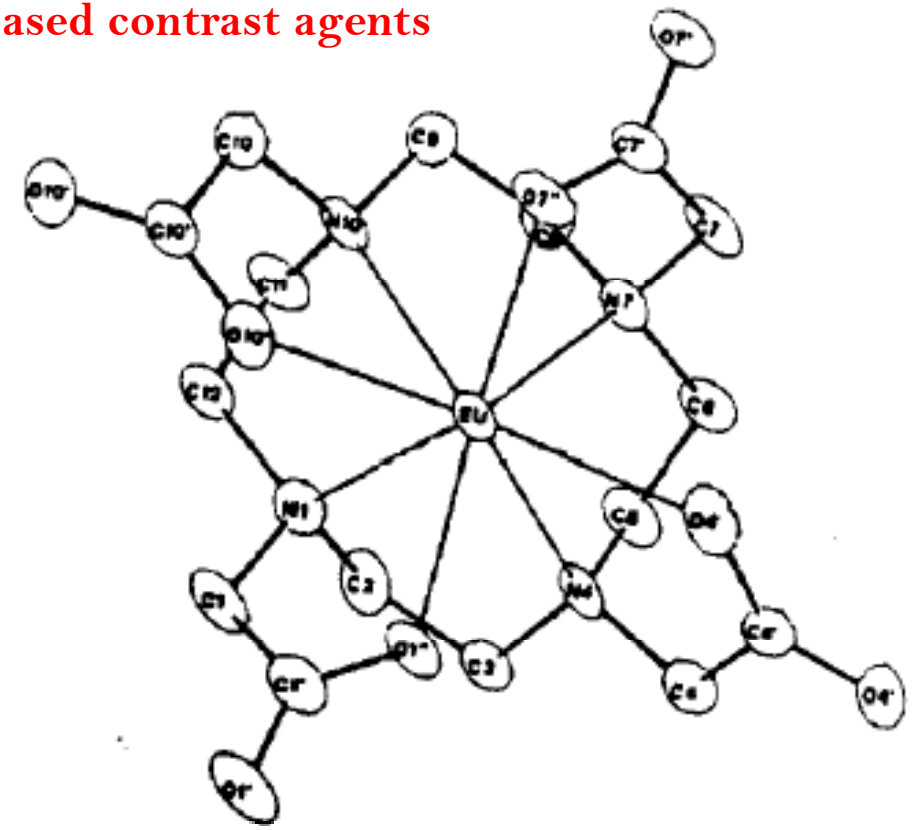
Complex problem in solvation dynamics and diffusion…

"Designing" MRI Ln-based contrast agents



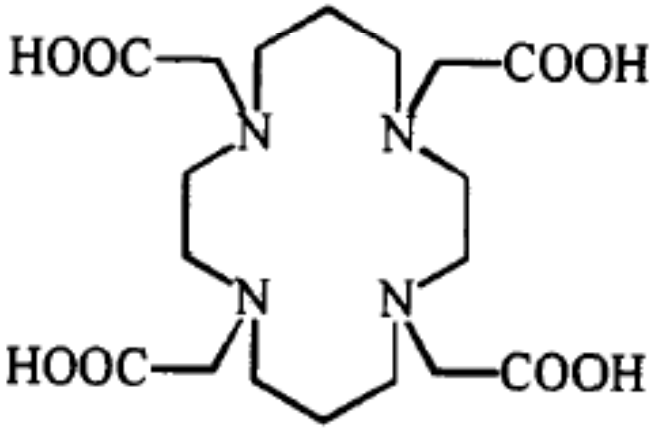
TADTA

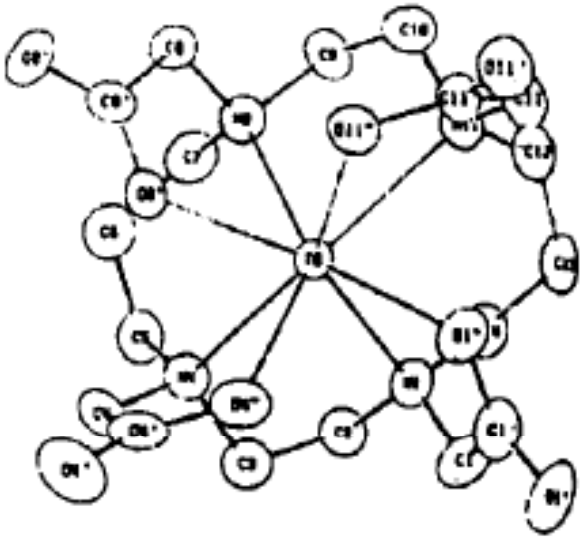
tetracarboxylates

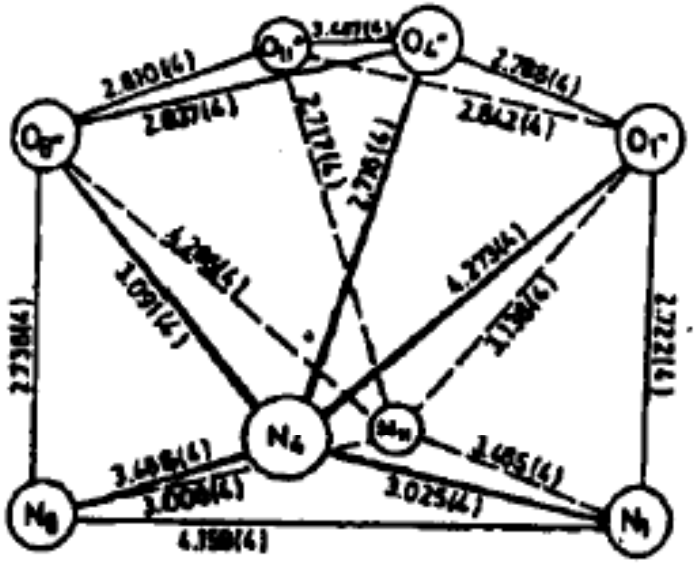


Rigid macrocyclic ring..stable! Its stability reduces the "toxicity" of the "free" metal ions in the human body…

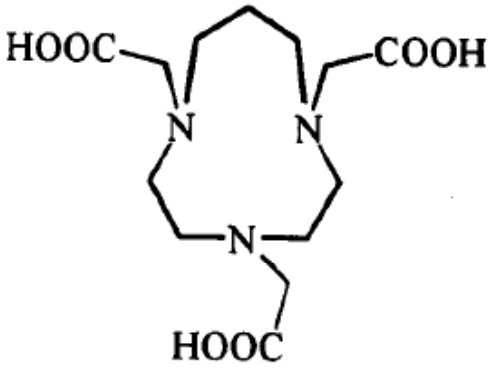
…but: - not many vacant positions available for water binding…
- ionic complexes result in increased osmotic pressure…


HOOC
COOH
N
N
N
N
HOOC
COOH

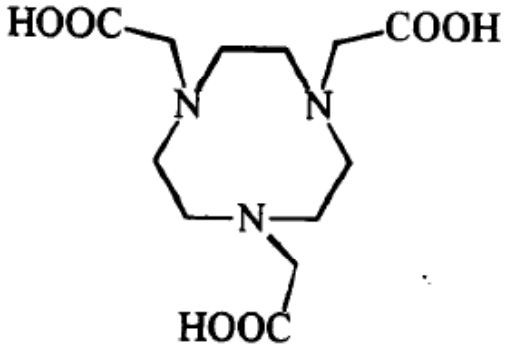




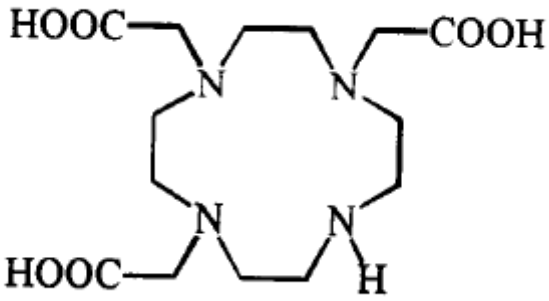
tricarboxylates…to make neutral complexes and avoid high osmotic pressure

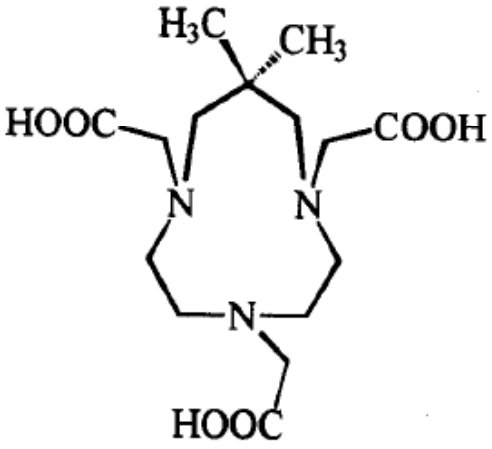


TANTAH$_3$

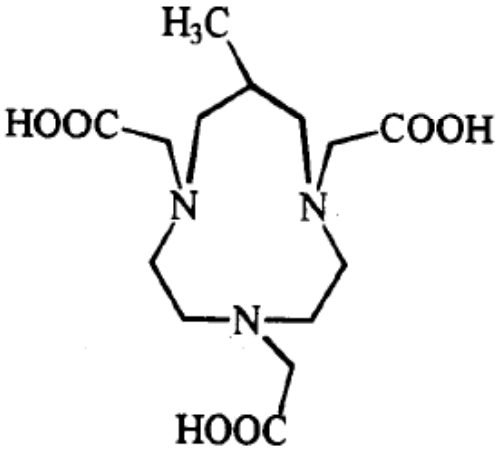


TRDTAH$_3$

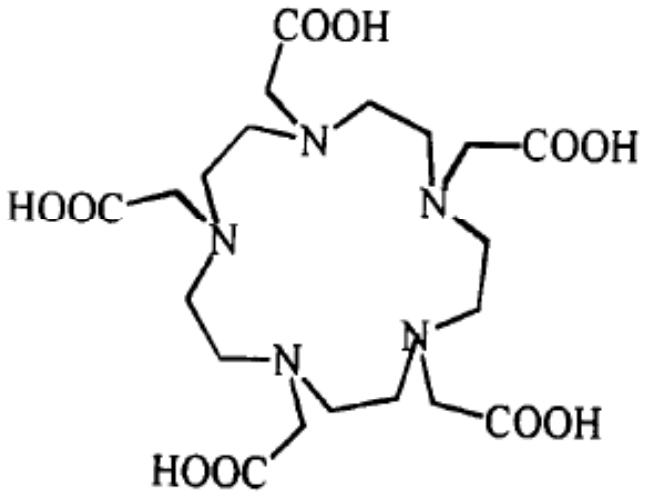


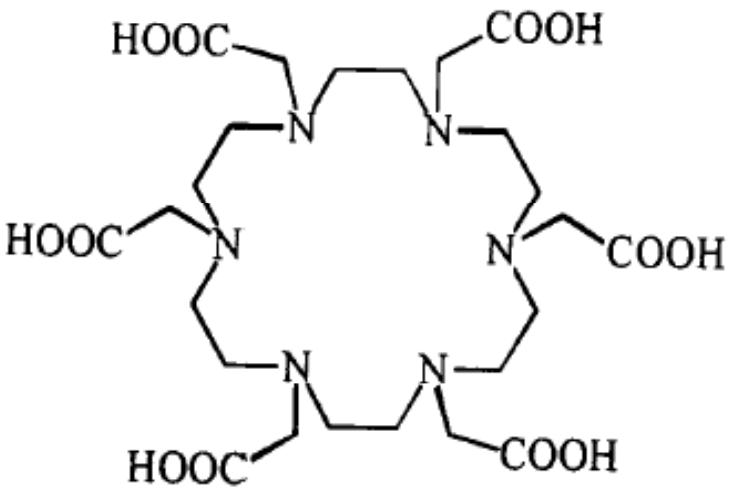


M-TRDTAH$_3$



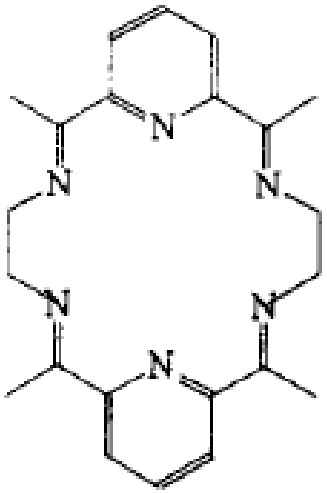
DM-TRDTAH$_3$



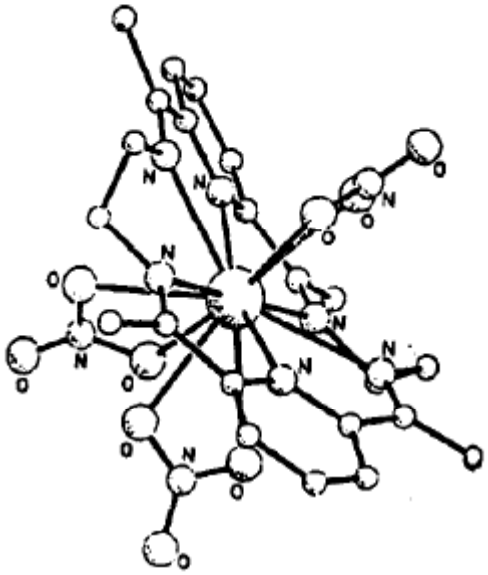


penta- and hexa-carboxylates…

…need for many vacant sites for the water to bind…



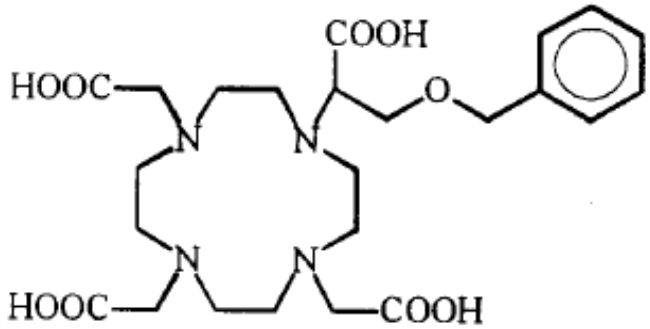
ACPYEN



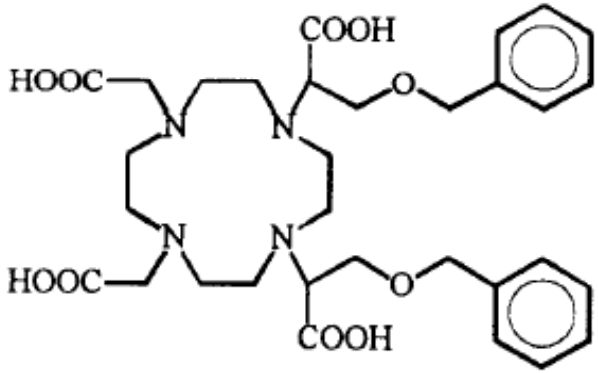
$[Gd(ACPYEN)(OAc)_2]Cl{\cdot}4H_2O$

Almost similar effect to T_2 as the Gd(III)(aq.) !!!

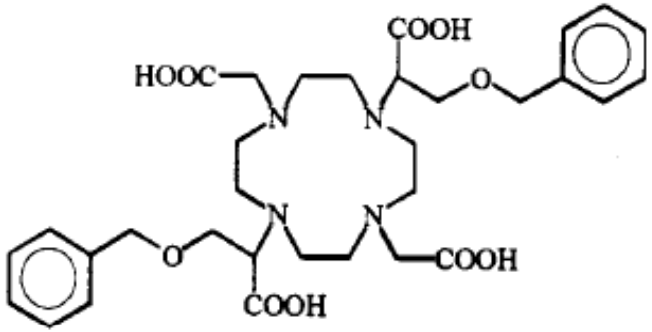
…remember that "Correlation times (r_c) depend on the size of the metal containing compound" and that "the bigger the molecule the smaller T_1 and T_2" ???



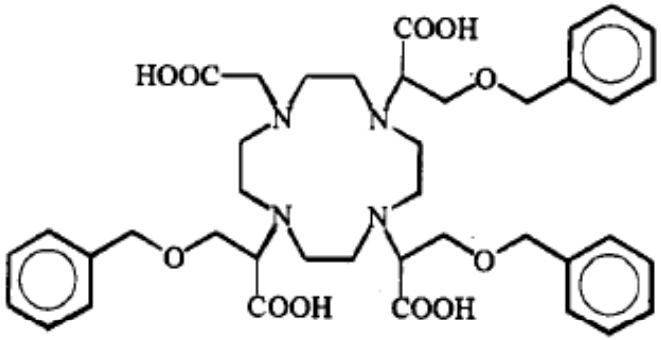
TADTA-LH$_4$



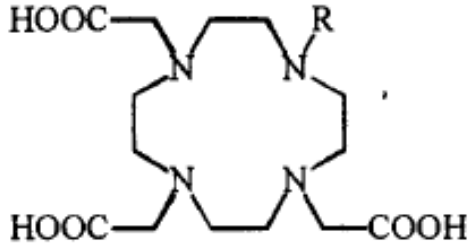
TADTA-C2LH$_4$

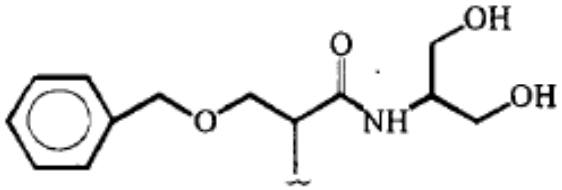


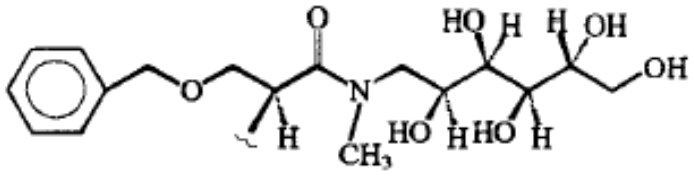
TADTA-T2LH$_4$

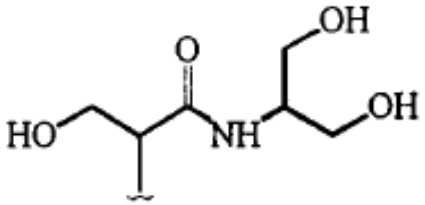


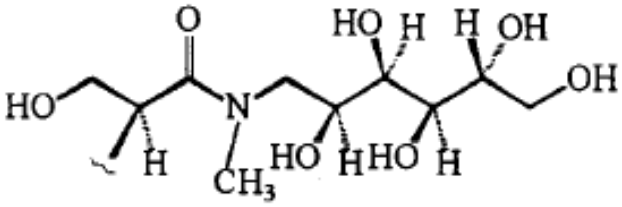
TADTA-3LH$_4$

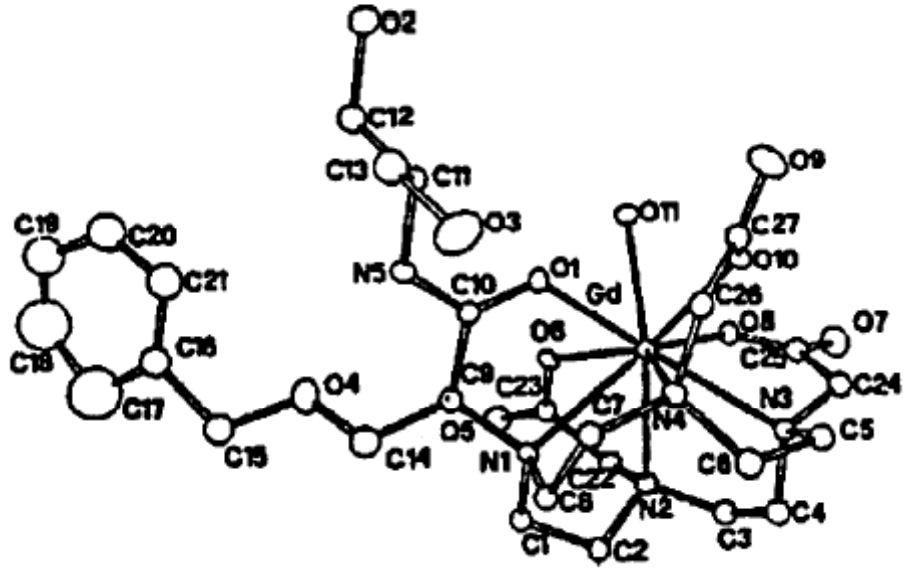

HOOC
R
HOOC
COOH


O
OH
NH
OH
O


O
HO H H OH
OH
O
N
H
HO H HO H
CH3

R_3= 
OH
O
HO
NH
OH

R_4= 
O
HO H H OH
HO
N
OH
H
HO H HO H
CH3


O2
C12
C13
C11
O3
O11
O9
C27
O10
C19
C20
C21
N5
C10
O1
Gd
C26
O8
O7
C25
C24
C18
C16
O6
C9
C23
N3
C17
O4
O5
C7
N4
C5
C15
C14
N1
C22
C6
C8
N2
C4
C1
C2
C3

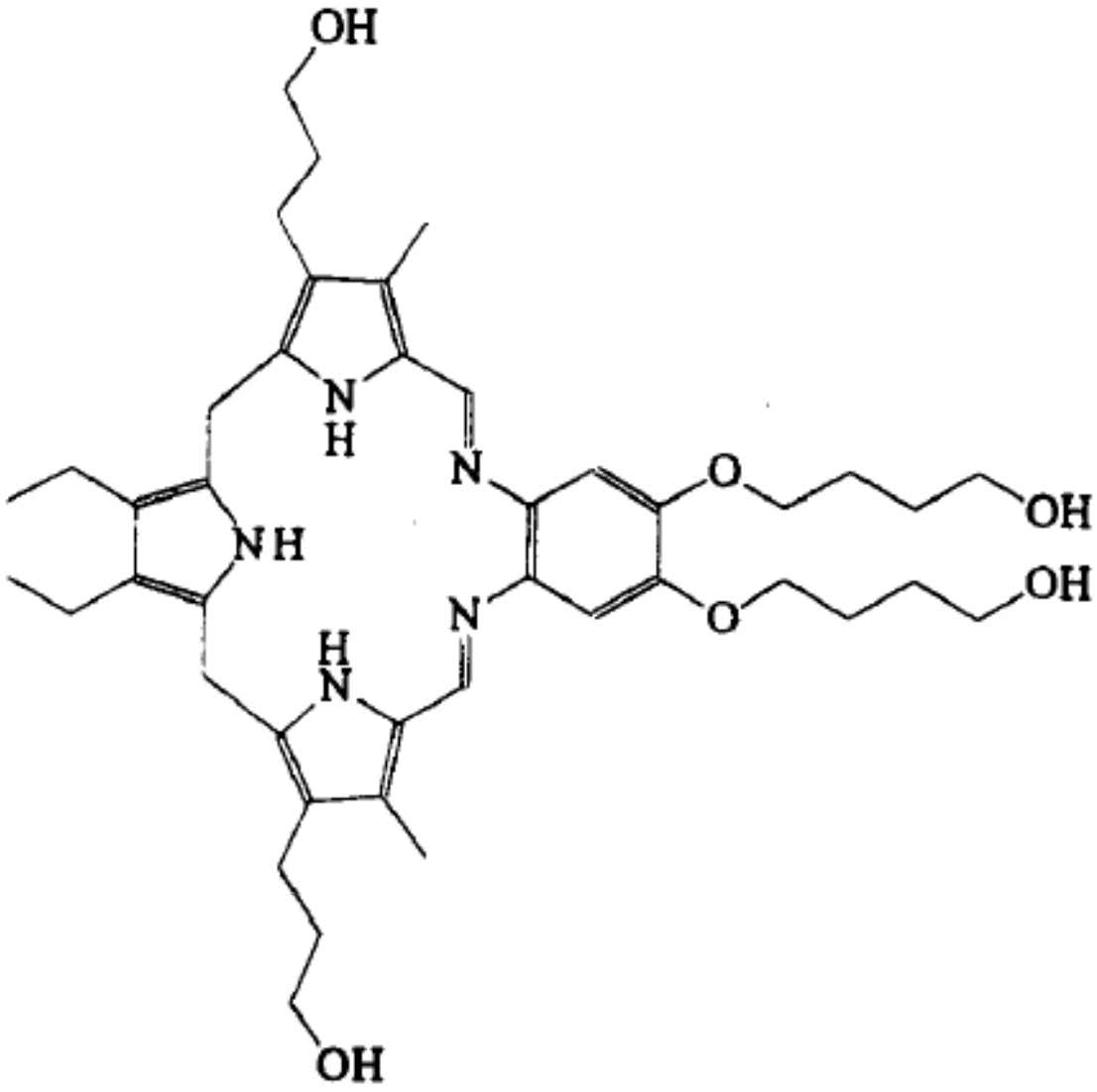

OH
N
H
N
NH
N
H
N
O
OH
O
OH
OH

TABLE I. Longitudinal Relaxivities (R_1) and the Number of Coordinated Water Molecules (q) for Low Molecular Weight Complexes

complex	q^a	R_1, $mM^{-1}\ s^{-1}$	freq, MHz	temp, °C	ref	complex	q^a	R_1, $mM^{-1}\ s^{-1}$	freq, MHz	temp, °C	ref
					Gd(III)						
aquo ion	8, 9	34.3	0.02	5	*b*			4.7	20	25	69
		26.5	0.02	25	*b*			3.4	20	37	7, 89
		22	0.02	35	69	DTPA	1	7.7	0.02	25	69
		21.4	10	5	*b*			6.7	0.02	35	70
		16.1	10	25	*b*			6.2	6.25	23	129
		9.1	20	35	69			5.6	10	23	125
		9.1	90	37	*c*			4.8	20	25	69
EDTA	2, 3	25	0.02	5	72			4.1	20	35	70
		15	0.02	25	69			3.7	20	37	7, 89
		12	0.02	35	70			4.5	20	37	118
		12	20	5	72	tris(dipic)	0	4.2	0.02	37	*d*
		7.6	20	25	69			2.6	20	37	*d*
		6.6	20	35	70	EGTA	u	3.4	20	30	*e*
		5.4	20	37	7, 89	TETA	0	3.3	0.02	37	69
		6.9	20	37	118			5.2	10	23	125
		4.6	90	37	*c*			2.1	20	37	69
DOTA	1	11.3	0.02	25	69			2.1	20	37	7, 89
		7.2	10	23	125	TTHA	0	2.0	20	37	7
					Mn(II)						
aquo ion	6	44	0.02	35	69	DOTA	u (0?)	2.6	0.01	25	69
		15.5	6.25	23	129			1.7	10	25	69
		7.4	20	35	69			1.1	20	37	7, 89
		8.0	20	37	*f*	DTPA	0	3.4	0.02	5	72
		6.3	40	rt	*g*			2.4	0.02	25	69
		7.4	60	20	74			2.1	0.02	35	70
		5.2	90	37	*c*			2.2	20	5	72
NTA	2	4.4	40	rt	*g*			1.5	20	25	69
EDTA	1	5.6	0.02	25	69			1.3	20	35	70
		4.8	0.02	35	70			1.1	20	37	7, 89
		3.3	20	25	69			1.6	60	20	76
		2.9	20	35	70	EGTA	0	1.7	60	20	85
		2.0	20	37	7, 89	NOTA	0	3.3	0.02	5	72
		3.3	40	rt	*g*			2.3	0.02	25	69
		3.3	60	20	74			2.3	20	5	72
		2.1	90	37	*c*			1.6	20	25	69
					Mn(III)						
acetate, tris	u	4.0	20	37	*f*			19	20	5	73
TPPS	2	6.9	0.02	5	73			15	20	20	73
		7.3	0.02	20	73			12	20	35	73
		7.8	0.02	35	73	[14]aneN$_4$	2	3.08	6.25	23	129

TABLE II. Selected Longitudinal Relaxivities (R_1) for Protein–Metal Ion Complexes and for Bovine Serum Albumin (BSA) Covalently Labeled with Metal Chelates

complex	R_1,[a] M^{-1} s^{-1}	freq, MHz	temp, °C	ref
	Gd(III)			
glutamine synthetase	148	22.5	25	*b*
immunoglobulin	112	20	19	*c*
concanavalin A	60	20	25	70
BSA	72	24.3	30	*d*
(BSA)$(GdEDTA)_n$[e]	36	20	37	88
EDTA (free)	6.6	20	35	70
$(BSA)(GdDTPA)_n$	19	20	37	88
DTPA (free)	4.1	20	35	70
	Mn(II)			
pyruvate kinase	275	20	25	28
concanavalin A	96	20	25	70
carboxypeptidase	43	20	25	28
$(BSA)(MnEDTA)_n$	26	20	37	88
EDTA (free)	2.9	20	35	70
$(BSA)(MnDTPA)_n$	3.4	20	37	88
DTPA (free)	1.3	20	35	70
	Fe(III)			
fluoromethemoglobulin	7.3	20	6	28
methemoglobin	1.4	20	6	28
transferrin	2.6	20	38	28
	Cr(III)			
transferrin	2.0	20	38	28

Keep in mind that Relaxivity in tissues depends on TWO main factors:

1) **The chemical environment encountered by the complex in vivo, and**

2) **the Compartmentalization of the tissue water…water in tissues exist: 5 % in intravascular space**
   15 % in interstitial space (between cells and capilaries), and
   80 % in intracellular space

This may lead to dicreased relaxivity rates, because all water may not be "seeing" the agent…

Key factors for improving relaxivity of the contrast agent

$$\left[\frac{1}{T_1}\right](\text{inner sphere}) = \frac{P_M q}{T_{1M} + \tau_M}$$

$$\frac{1}{T_{1M}} = \frac{2}{15}\frac{\gamma_I^2 g^2 S(S+1)\beta^2}{r^6}\left[\frac{7\tau_c}{(1+\omega_S^2\tau_c^2)} + \frac{3\tau_c}{(1+\omega_I^2\tau_c^2)}\right] + \frac{2}{3}S(S+1)\left(\frac{A}{\hbar}\right)^2\left[\frac{\tau_e}{1+\omega_S^2\tau_c^2}\right]$$

q: number of H_2Os bound per metal

***r*: proton – metal distance**

r_c: correlation time…rotation, tumbling, …

T_{1e}: longitudinal e^- spin relaxation time

τ_M: residence lifetime of bound water

Stability and Toxicity of the contrast agent

TABLE IV. Acute LD_{50} Values for Metal Salts, Meta Complexes, and Free Ligands

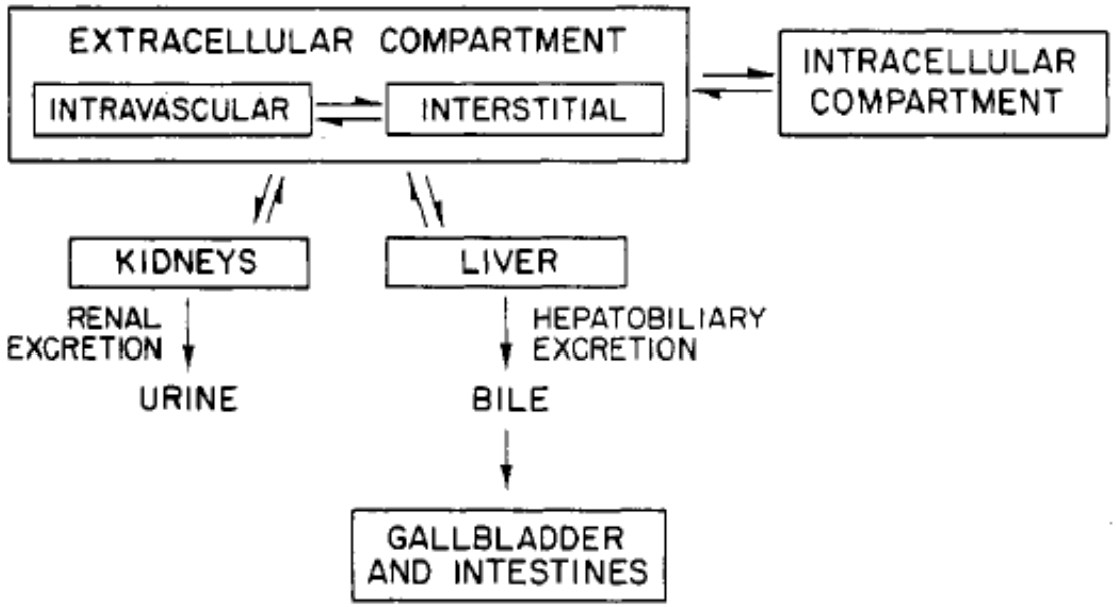
compound	LD_{50}, mmol/kg	animal	admin[a]
$GdCl_3$	0.5	rat	iv
	0.4	mouse	iv
	0.26	rat	iv
	1.4	mouse	ip
$Gd(OH)_3$	0.1	mouse	iv
$(MEG)[Gd(EDTA)(H_2O)_n]$[c]	0.3	rat	iv
	0.62	mouse	ip
$MEG[Gd(CDTA)(H_2O)_n]$	<2.5	rat	iv
$MEG[Gd(EGTA)(H_2O)_n]$	<2.5	rat	iv
$(MEG)_2[Gd(DTPA)(H_2O)]$	10	rat	iv
	>10	mouse	iv
$Na_2[Gd(DTPA)(H_2O)]$	>10	mouse	iv
	20	rat	iv
$(MEG)[Gd(DOTA)(H_2O)]$	>10	mouse	iv
$Na[Gd(DOTA)(H_2O)]$	>10	mouse	iv
$(MEG)_3[Gd(TTHA)]$	6	rat	iv
$MnCl_2$	0.22	rat	iv
	1.5	mouse	ip
$Na_2[Mn(EDTA)(H_2O)]$	7.0	rat	iv
	5.9	mouse	ip
$Na_3[Mn(DTPA)]$	1.9	rat	iv
$Mn(III)(TPPS)^{3-}$	~0.5	mouse	iv
$FeCl_3$	1.6	mouse	ip
$Na[Fe(EDTA)(H_2O)]$	3.4	mouse	iv
	1.7	mouse	ip
$Na_3[Ca(DTPA)]$	5.0	rat	iv
	3.5	mouse	iv
$(MEG)_3H_2DTPA$	0.15	mouse	iv
Na_2H_3DTPA	0.1	mouse	iv
$Na_2[Ca(DOTA)]$	>7.0	mouse	iv
$(MEG)_2H_2DOTA$	0.18	mouse	iv

[a] Route of administration: iv = intraveneous; ip = intra neal. [b] *Registry of Toxic Effects of Chemical Substances*; N Institute of Occupational Safety and Health; U.S. Gove Printing Office: Washington, DC, 1982. [c] MEG = *N*-meth amine. [d] Weinmann, H.-J., unpublished results. [e] Tweedle unpublished results.

LD stands for "Lethal Dose". LD_{50} is the amount of a material, given all at once, which causes the death of 50% of a group of test animals.

The smaller the LD_{50} value, the more toxic the chemical is. The opposite is also true: the larger the LD_{50} value, the lower the toxicity.

Table 2: Toxicity Classes: Gosselin, Smith and Hodge		
Probable Oral Lethal Dose (Human)		
Toxicity Rating or Class	Dose	For 70-kg Person (150 lbs)
6 Super Toxic	Less than 5 mg/kg	1 grain (a taste - less than 7 drops)
5 Extremely Toxic	5-50 mg/kg	4 ml (between 7 drops and 1 tsp)
4 Very Toxic	50-500 mg/kg	30 ml (between 1 tsp and 1 fl ounce)
3 Moderately Toxic	0.5-5 g/kg	30-600 ml (between 1 fl oz and 1 pint)
2 Slightly Toxic	5-15 g/kg	600-1200 ml (between 1 pint to 1 quart)
1 Practically Non-Toxic	Above 15 g/kg	More than 1200 ml (more than 1 quart)


EXTRACELLULAR COMPARTMENT
INTRAVASCULAR
INTERSTITIAL
INTRACELLULAR COMPARTMENT
KIDNEYS
LIVER
RENAL EXCRETION
HEPATOBILIARY EXCRETION
URINE
BILE
GALLBLADDER AND INTESTINES

Ok…besides the C.A., is everything else safe???

10.2 Radiofrequency effects

- The main effect of RF exposure is tissue heating. This is restricted to less than 1 °C by monitoring and limiting the SAR (specific absorption rate). Care is required to avoid the heating of leads used for physiological monitoring.
- Peripheral nerve stimulation (PNS) is the main bioeffect of the time-varying magnetic fields generated by the gradients. It may cause discomfort but it is not harmful. Modern scanners have a stimulation monitor to alert the user to the likelihood of causing PNS.

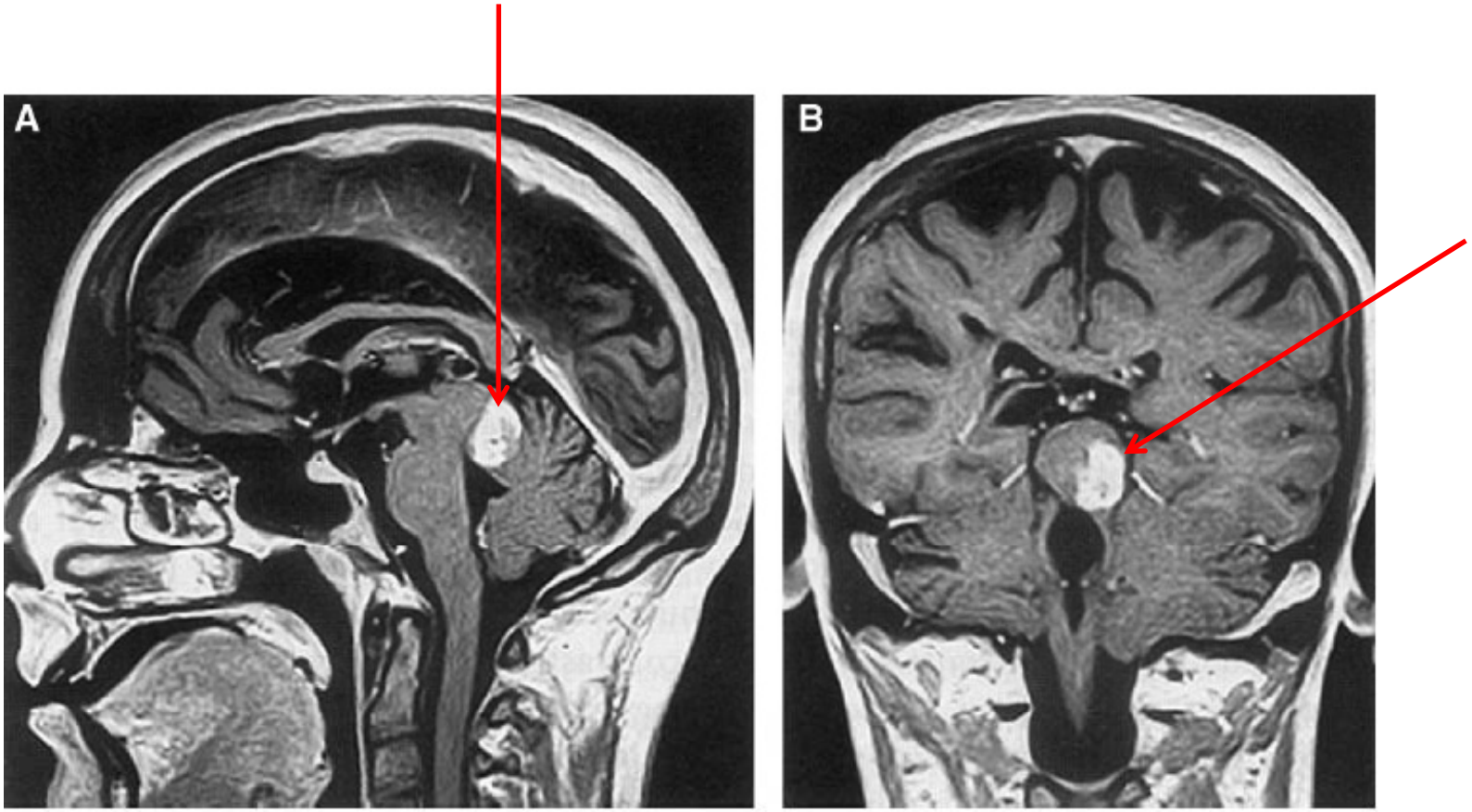
Table 4 *Soluble MRI contrast agents*

Names[a]	*Manufacturer*[a]	*Formula*
AngioMARK® (renamed Vasovist®) Gadophostriamine trisodium	Mallinckrodt/Tyco Healthcare	$Na_3[Gd(MS\text{-}325)(H_2O)]$
Dotarem® Gadoterate meglumide	Guerbet	$(NMG)[Gd(dota)(H_2O)]$
Eovist® (renamed Primovist®) Gadoxetic acid disodium	Schering	$Na_2[Gd(dtpa\text{-}eob)(H_2O)]$
Gadovist® Gadobutrol	Schering	$[Gd(do3a\text{-}butrol)(H_2O)]$
Magnavist® Gadopentetate dimeglumide	Schering	$(NMG)_2[Gd(dtpa)(H_2O)]$
Multihance® Gadobenate dimeglumide	Bracco	$(NMG)_2[Gd(bopta)(H_2O)]$
Omniscan® Gadodiamide	GE Healthcare (previously Nycomed-Amersham)	$[Gd(dtpa\text{-}bma)(H_2O)]$
OptiMARK® Gadoversetamide	Mallinckrodt/Tyco Healthcare	$[Gd(dtpa\text{-}bmea)(H_2O)]$
Prohance® Gadoteridol	Bracco	$[Gd(hp\text{-}do3a)(H_2O)]$
Lumenhance®	Bracco	$MnCl_2$
Teslascan®	GE Healtcare (previously Nycomed-Amersham)	$Na_3[Mn(Hdpdp)]$

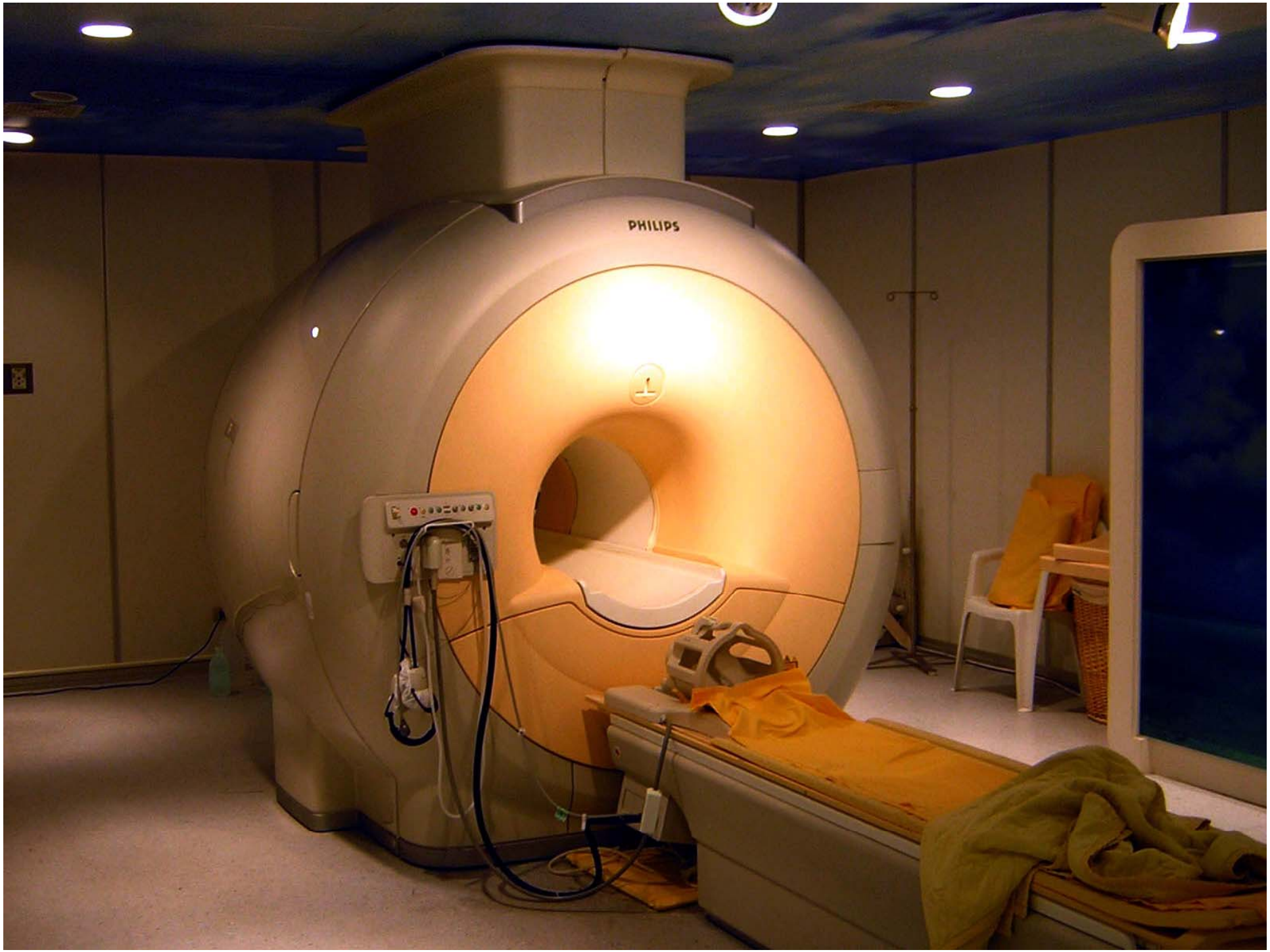
Table 5 *Comparison of data for four MRI contrast agents*

Complex[a]	*Gd(hp-do3a)*	*Gd(dtpa-bma)*	*Gd(dtpa)*$^{2-}$	*Gd(dota)*$^{-}$
log *K*	23.8	17.1	22.2	25.3
log *K**[b]	17.1	14.9	17.8	18.3
r (Gd--H) (pm)	250	242	249	246
Rotation time[c] τ_R (s^{-1})	57	53	55	63
Water exchange rate (s^{-1})	2.86×10^6	0.45×10^6	3.3×10^6	4.10×10^6
Relaxivity r_1 ($mM^{-1}\ s^{-1}$)	3.7	3.8	3.8	3.5
Osmolality (37°C)[d]				
0.5 M solution (Osmol kg^{-1})	0.63	0.65	1.96	1.35
1.0 M solution (Osmol kg^{-1})	1.91	1.90	5.85	4.02
Viscosity (37°C)				
0.5 M solution (cP)	1.3	1.4	2.9	2.0
1.0 M solution (cP)	3.9	3.9	>30	11.3
Dissociation[e] $t_{1/2}$ (min)	*ca.* 180	*ca.* 0.5	10	$> 4 \times 10^5$
LD_{50}[f] (mmol kg^{-1})	12	15	6	11
Reaction[g] Cu^{2+}	< 1%	35%	25%	< 1%
Reaction[g] Zn^{2+}	< 1%	25%	21%	< 1%
Whole body Gd at 1 day[h]	2	2	2	2
Whole body Gd at 7 days[h]	0.05%	1%	0.2%	0.1%
Whole body Gd at 14 days[h]	0.03%	1%	0.1%	0.05%

[a] Each complex is thought also to coordinate 1 water molecule not shown in the formula.
[b] Conditional stability constant at pH 7.4.
[c] Correlation time for molecular rotation.
[d] Osmolality represents the sum of the molalities of the osmotically active solutes present.
[e] Approximate half life for dissociation at pH 1.
[f] Values for rodents.
[g] The percentage of free Gd^{3+} released over 10 min at 22°C when the complex is challenged with 25 mM Cu^{2+} or 25 mM Zn^{2+} ions in the presence of 66 mM phosphate at pH 7.
[h] Residual whole body ^{153}Gd (%) in mice after intravenous injection of radiolabelled complex at 0.4 mmol/kg^{-1} body weight.

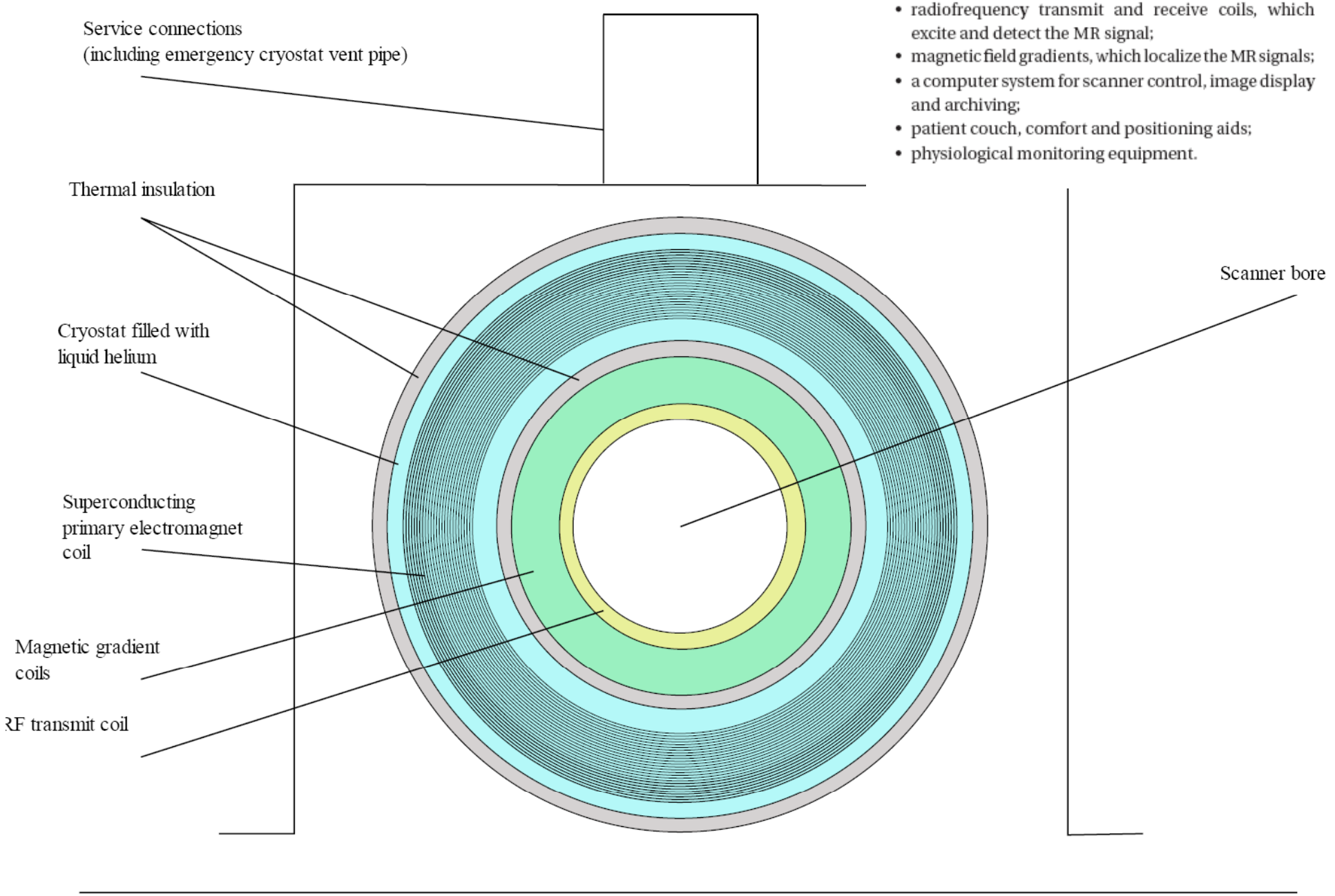


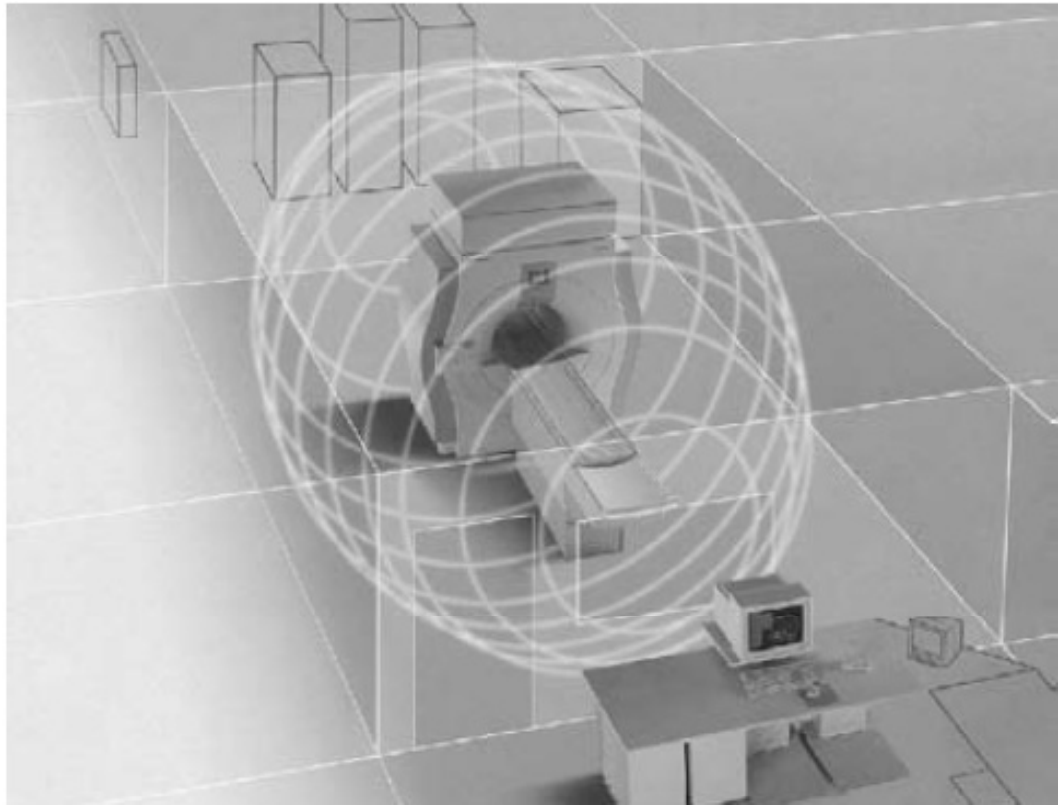
A T_1 weighted image obtained after intravenous injection of ProHance® (0.1 mmol kg^{-1}) showing a Tectal glioma as the white region just to the right of centre in the Saggital image A and the coronal image B


PHILIPS

The MR system itself consists of:

- a magnet that produces a strong, constant magnetic field;
- radiofrequency transmit and receive coils, which excite and detect the MR signal;
- magnetic field gradients, which localize the MR signals;
- a computer system for scanner control, image display and archiving;
- patient couch, comfort and positioning aids;
- physiological monitoring equipment.





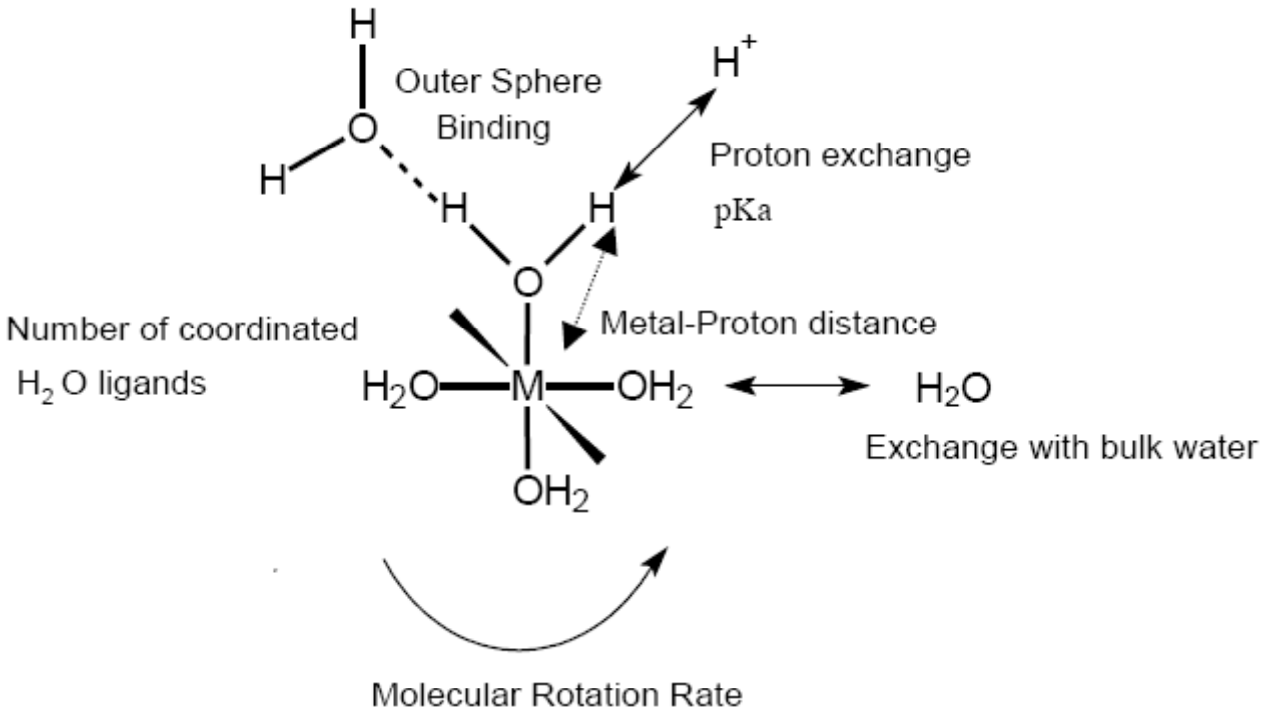
What to remember…

There are two important contributions to the relaxivity effects:

Inner sphere

Outer sphere

For both to be present there must be at least one binding site for water at the gadolinium centre.



The factors which affect the relaxivity of a paramagnetic complex.

Why do you need a contrast agent ?

Provides an improved image allowing you to see previously unclear features – very important in diagnosis.

Magnevist was approved in 1988 and since then increased to about 40% of scans use a contrast agent.

Predicted to rise as new agents and applications appear.

Cost: £60 a bottle (per scan)

Literature

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4) *MRI: From Body to Proton*, D. W. McRobbie, E. A. Moore, M. J. Graves and M. R. Prince, 2nd ed., Cambridge University press, 2006.

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