



Medical Diagnosis by Nuclear Magnetism

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Diagnosis by external exploration has made continual progress ¹⁾ from the discovery of X-ray radiography to the present day tomography in its most elaborate version, the EMI-Scanner (computerized transverse axial scanning). By means of this last apparatus, it has become possible to explore blocks of tissue down to a volume of less than 1 mm³ in a sample as big as the human body, and determine variations in density of the order of 10⁻³ and of atomic number of the order of 2 · 10⁻³. It is thus possible, relatively rapidly, to plot the cross-section of a given part of the human body to determine if certain pathological anomalies are present. The inherent dangers of the use of ionizing rays and the cost of such apparatus however, limit their use.

Ultrasonic imaging constitutes a different approach to the problem. Operating on the changes in reflection coefficient of ultrasound at the surfaces separating tissues, it gives a « visualization » of these surfaces and the organs which they limit. The danger of the excitations produced by ultrasound seems limited and moreover, the cost of the apparatus is considerably lower than that of the EMI-Scanner. The present major application of ultrasonic imaging is in obstetrics.

Physical Background of Nuclear Magnetic Diagnostics

Some years ago, a new method again was proposed, that of diagnostics by nuclear magnetic resonance (NMR). Without discussing the principles of NMR ²⁾ it is to be noted that a sample to be analysed is submitted

to a constant magnetic field H_0 and to a radiofrequency field. This radiofrequency field is orthogonal to H_0 and its pulsation is determined by the magnitude of H_0 and by certain characteristics of the nuclei of the atoms of the sample (magnetic moment, spin...). One can then observe a signal whose maximum amplitude is proportional to the magnetization of the nuclei in the field H_0 . Thus, for instance, water contains protons characterized by a certain magnetic moment and spin. Placed in a magnetic field $H_0 = 1$ T, they have a resonance at the frequency ~ 42 MHz, the Larmor frequency.

The free precession opens another way to studying nuclear magnetism and can be used in weak fields. As originally conceived, the technique consisted of placing the sample in a « polarizing » field (5 to 10 mT) perpendicular to the direction of the earth's magnetic field. A rapid cutting of the polarizing field (of duration of the order of the Larmor period) allowed the precession around the axis of the earth's field to be observed. If the sample is water and the earth's field of the order of 0.05 mT, the precession frequency of the protons is about 2 kHz ³⁾.

Compared to the other techniques (X-ray, ultrasound) this new diagnostic method has two essential distinguishing features :

1) Instead of giving a map of the tissues based on the static properties (absorption coefficient or reflection coefficient of the nuclei, atoms or molecules), it gives information about the dynamics of the magnetic energy exchanges between the nuclei under

investigation (most often by the protons of the water molecules) and their environment. This energy transfer is characterized by time constants, the *relaxation times* :

— spin-lattice T_1 : transfer of magnetic energy of nuclei to the molecular motion ;

— spin-spin T_2 : transfer of magnetic energy between the nuclei themselves.

The relaxation times are sensitive to the molecular motion itself, thus permitting the correlation times τ_i or diffusion constants D_i ($i = 1, 2, \dots$) to be deduced characterizing the mobility of the molecular environment.

2) Thus while X-ray or ultrasound only exploits one parameter (absorption or reflection coefficient), the observation of nuclear magnetism permits the determination of *several parameters* which characterize the molecular motions and energy exchanges in a given biological environment ; accordingly, it makes possible a much more precise identification of the surrounding medium.

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Table 1 — Damadian's first results

	Normal liver	Novikoff hepatoma	Walker sarcoma
T_1, s	$0,293 \pm 0,01$	$0,826 \pm 0,013$	$0,736 \pm 0,022$
T_2, s	$0,052 \pm 0,003$	$0,118 \pm 0,002$	0,100

In water of ordinary temperature (20°C) for example, $T_1 \sim T_2 = 2.5$ s while for ice $T_1/T_2 \sim 10^5$. Viscosity or the presence of paramagnetic ions can diminish the relaxation times in liquids by a factor 10^3 or even 10^4 . Moreover, also the diffusion constants can vary over a large range.

Cancerous Tissues and Spin Mapping

Historically, diagnosis by NMR is based on a discovery by R. Damadian ⁴⁾ that the relaxation times of the protons of water molecules in cancerous tissue from rats, measured in the conventional domain ($H_0 = 0.56$ T) are appreciably longer than those obtained from measurements on the same kind of sound tissue.

This discovery initiated a considerable number of publications, which have confirmed Damadian's conclusions with respect to human tissues. They have, however, also shown that :

- the difference in relaxation time is often much smaller than in the example given in Table 1 — even too small (or indeed in the opposite sense) to admit presently the use of this technique for the diagnosis of cancer.
- the intermolecular mechanisms being at the origin of this difference are still incompletely understood, and there is no general agreement on their interpretation.

In spite of these difficulties, studies on the subject become more and more numerous and whether devoted to cancer or other pathological extracts indicate a promising development.

The study of living tissues, especially those belonging to complex organisms poses a second problem : the necessity to explore only homogeneous samples of small volume if one wants to obtain useful information. The proposed techniques (Zeugmatography, spin mapping, spin-imaging, fonar ⁵⁾ ...) permits, by means of an adjustable system of inhomogeneous magnetic fields, superposed on the field H_0 , the reception of signals from a small portion of the sample only. One has thus managed to explore mm^3 by mm^3 of a living biological system for which the section

could attain 50 cm^2 . Recently, Lauterbur, Mansfield, Damadian, Hinshaw and collaborators presented real "radiographies" of soft living tissue ⁶⁾.

In Fig. 1 the image is shown of a thin cross-section near the roots of a reasonably fresh spring onion. The apparent height of the image is proportional to the density of free water at the corresponding point in the sample. The outer rings and wet central region are clearly visible ¹²⁾.

The aim of these efforts is evidently the extension of this kind of diagnostics to tissues of the human body *in situ*. The minimal or perhaps non-existent danger associated with exposing the human body to constant magnetic fields, or varying fields of weak intensity, has stimulated efforts towards the construction of spectrometers able to receive the human body as a sample. Actual projects are centred on instruments working at between 1 and 5 MHz (H_0 between 25 and 100 mT). Although the apparatus of Lauterbur is quite close to being able to do this (distance between the poles 62 cm, $H_0 = 100$ mT and $\omega_0 \sim 4$ MHz) none is capable of receiving a human body for the present. The technical problems will not be resolved either easily or cheaply and the method does not eliminate entirely the risks associated with the action of such fields on patients. Precautions recommended by the security services of the laboratories where

similar big magnets are used ⁷⁾, indicates that one should show a certain prudence. These difficulties thus might postpone the use of the technique for diagnostic work on living humans.

Magnetography in Weak Fields

Another possibility is that of exploiting nuclear magnetism in the weak field range (0.5 — 0.05 mT) the motivation being that in this case, the engineering difficulties and biological dangers are greatly diminished. For the past twenty years a group in Geneva has been exploring the techniques of using the free precession in the earth's magnetic field after prepolarisation, and nuclear magnetic resonance in weak fields (0.2 — 1.0 mT). These techniques seem to offer possible answers to the problems posed, as the preliminary studies which have been done on biological tissues are highly promising.

It will be noted that these techniques permit the determination of the same parameters as do those of the strong field. Also, it is easy to vary within relatively large limits, the value of H_0 (normally the prepolarisation can attain 10 mT, the earth's field is 0.05 mT). One thus measures the constants T_1 and T_2 in the rotating frame with effective fields of only some microtesla. This large field range makes it possible to obtain the correlation times in the domain where

Fig. 1 Cross-section of a spring onion as seen by NMR.

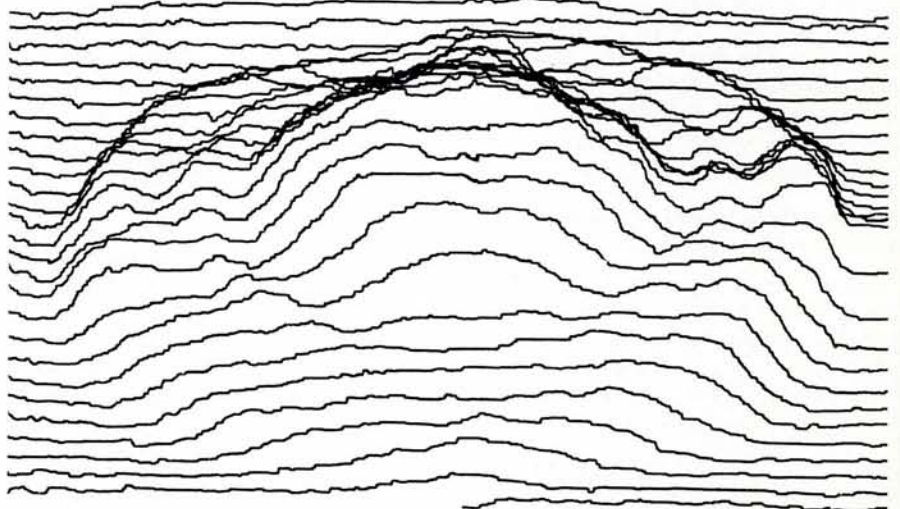


Table 2 — Experimental results of weak field magnetography

		T_1	T_2, s
Blood	normal	0.3	0.1
amniotic fluid ⁹⁾	normal	2.5-1.6	2.0-1.3
(28 samples)	pathological	1.9-1.5	1.3-0.9
pleural fluid ¹⁰⁾	normal	1.6	1.1
(12 samples)	pathological	0.9-0.5	0.6-0.3
peritoneal fluid	normal	1.4	1.1
(1 sample)			

they are most sensitive to the chemo-biological bindings (200 kHz — 20 Hz). Moreover with the weak field it is easy to obtain a homogeneous field over quite big volumes, to which the sample (human body) can be submitted with relatively easy access for both it and the necessary detecting devices.

A difficulty of the weak field apparatus is its relatively low sensitivity compared to that of NMR working in the conventional domain. It is well known that nuclear magnetic signals are roughly proportional to the square of the Larmor frequency, so that going from the conventional domain to the weak field, we lose a factor $10^7 - 10^9$ in sensitivity. Experiments in our laboratory show however, that despite this handicap, it is possible to work on biological samples of volume inferior to 10 cm^3 . Except in particularly favourable cases, an improvement on this performance, can be had only at the cost of the duration of the measurement.

Some experimental results will illustrate the possibilities described above :

Free precession after prepolarization is well suited to the measurement of T_2 on samples of large volume, especially in the human body. One has been able to explore a spectrum of values for T_2 going from 40 ms to the order of 1 s. Some measurements have been done on extracted tissues, others on tissues *in situ* (of one of the research staff⁸⁾). By free precession we can also measure T_1 but, the minimum value is now of about 300 ms. Because of the distribution of values of T_1 and T_2 in biological body liquids (0.1 — 2.5 s) in sound or pathological tissues, the position of the detection coil, the amplitude and the relaxation constants of the free precession signal are able to give information on the position, volume and nature of a pathological accumulation or transformation of *in situ* human body liquids.

Conclusions

The influence of pathological states on the value of the constants $T_1, T_2, \tau_1, D_1, \dots$ and the large spectrum of these values, suggest that there is a future for the application of these techniques to the external exploration of pathological changes, particularly as the methods are without danger to the patient.

Two possible developments can be envisaged :

- 1) Making a map of living tissues in a given area, based on the intensities of NMR signals recorded as these are mainly determined by the time constants of the relaxation effects. With such a dynamical method, a diseased part of a macroscopic tissue can appear on a screen which records the amplitude of the NMR signal point by point, the saturation phenomena associated with the relaxation being directly connected to the observed amplitudes¹¹⁾.
- 2) By a more careful examination of a sufficiently extended diseased tissue, determining the different time constants which have been mentioned may permit a precise identification of the pathological state.

The first of these methods supposes good resolution for big samples, the second one good sensitivity at low frequencies.

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