**RadioGraphics index terms:**
**Magnetic resonance imaging**
**TECHNICAL**
**Neurologic imaging**
**BRAIN**
**Radiation Physics**
**MAGNETIC RESONANCE IMAGING**

**Cumulative index terms:**
**Hemorrhage, MR studies**
**Brain, hemorrhage**


THIS EXHIBIT WAS DISPLAYED AT THE 72ND SCIENTIFIC ASSEMBLY AND ANNUAL MEETING OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA, NOVEMBER 30–DECEMBER 5, 1986, CHICAGO, ILLINOIS. IT WAS RECOMMENDED BY THE NEURORADIOLOGY PANEL AND WAS ACCEPTED FOR PUBLICATION AFTER PEER REVIEW AND REVISION ON JULY 31, 1987.

From the Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia.

(*) Presently at the Department of Radiology, Hadassah Hospital, Jerusalem, Israel.

Address reprint requests to R. I. Grossman, M.D., Neuroradiology Section, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

# Mechanisms responsible for the MR appearance and evolution of intracranial hemorrhage

John M. Gomori, M.D.*

Robert I. Grossman, M.D.

***The sequential degradation products of hemoglobin in an evolving hemorrhage are described here, and the physical mechanisms underlying their MR imaging characteristics are discussed.***

## Introduction

The hemoglobin in extravasated blood (hemorrhage) undergoes a predictable sequence of chemical degradations. The degradation products are paramagnetic and for a variety of reasons their relaxation rates following exposure to a strong external magnetic field and an RF pulse differ from those of the normal surrounding brain. Since MR signal intensity is a function of the relaxation rate of the substance imaged, hemoglobin degradation products and, hence, hemorrhage is distinguishable from normal brain on MR images. Moreover, since the degradation product present at a particular time and its spatial distribution are a function of the age of the hemorrhage, it is usually possible to distinguish between acute, subacute and chronic hemorrhage with MRI.

The purposes of this article are: (1) to define the sequential chemical degradation of hemoglobin in an evolving hemorrhage, (2) to elucidate the physical mechanisms that affect the relaxation rates of the various degradation products, and (3) to specify the dependence of these physical mechanisms on one's choice of field strength and pulse sequence.

The clinical MR images of evolving hemorrhage, the biologic factors that affect those images and the variety of vascular lesions in which they may be encountered are the subjects of the following article.

## The Sequential Degradation of Hemoglobin

The acute hemorrhage (blood collection) consists of intact red cells and plasma. The plasma is resorbed and, depending on the pH and $pO_2$, the hemoglobin becomes desaturated. With time, the hemoglobin is converted by oxidation to methemoglobin and the red cells lyse. Methemoglobin is eventually degraded and resorbed, and some of its iron is converted to ferritin and hemosiderin in the adjacent reactive macrophages (Figure 1). These macrophages persist for a long time if the blood brain barrier is intact. The iron of some states of hemoglobin and its derivatives is paramagnetic because it has unpaired electrons. This profoundly affects the MR image.

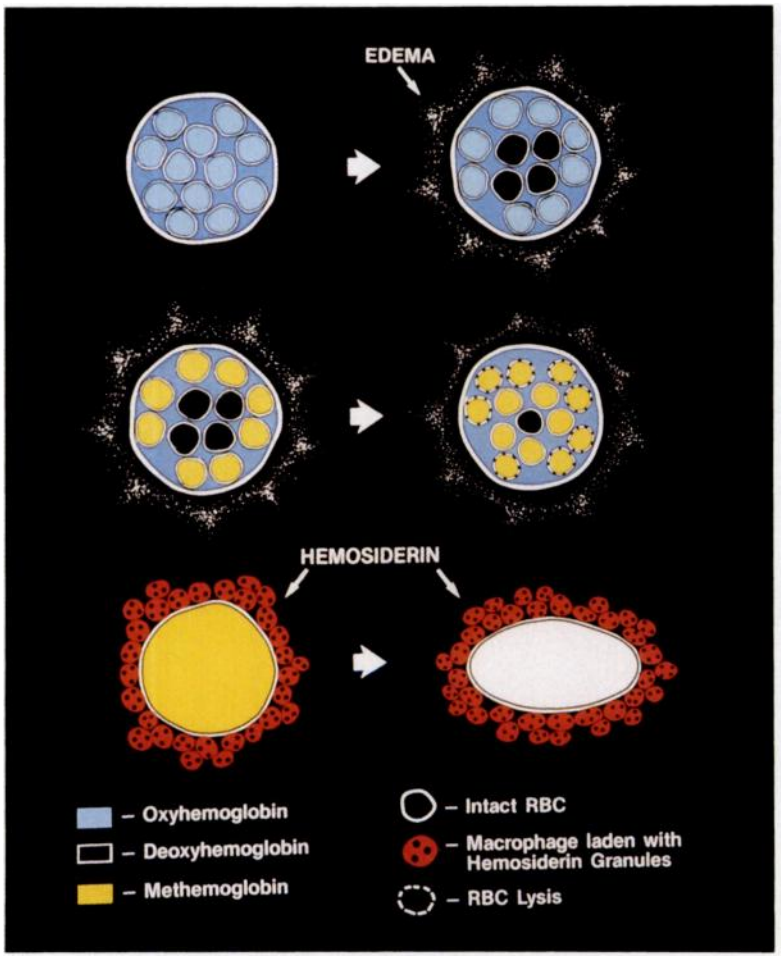



**Figure 1**
Evolution of intraparenchymal hemorrhage.
(See page 442.)

## Physical Mechanisms that Affect the Relaxation Rates of Hemoglobin Degradation Products

### MAGNETIC SUSCEPTIBILITY

Both the proton and electron are charged particles with spin ½ (the unit of quantized angular momentum). The momentum and electric charge of the proton and electron result in a magnetic moment; i.e., they are magnetic dipoles (north and south magnetic poles separated by a distance). The electron's lighter mass, about one-thousandth of the proton's mass, gives it a magnetic moment 1,000 times larger. In the absence of an external field, the electron magnetic dipoles of a paramagnetic substance point randomly in all directions, resulting in zero net magnetization. When an external field is applied, the strength of the field will be augmented because some of the unpaired electrons will align with the applied magnetic field. The ratio of the additional field strength to the strength of the applied field is called the magnetic susceptibility of the paramagnetic substance. It is an indication of how easily it can be magnetized. If a paramagnetic atom has N unpaired electrons, its magnetic susceptibility is proportional to (N)(N+2).

Eq. 1 $\chi$, magnetic susceptibility, $\propto$ (N)(N+2)

The T2 relaxation rate of a paramagnetic substance varies as the square of its magnetic susceptibility.

### PROTON-ELECTRON DIPOLE-DIPOLE PROTON RELAXATION ENHANCEMENT

In the absence of unpaired electrons, the protons of water molecules relax (realign with the magnetic field) via fluctuations in their local magnetic fields caused by the motion of adjacent protons. Adjacent unpaired electrons, because of their larger magnetic moment create fluctuations in local magnetic fields 1,000 times larger than those produced by the motion of protons. These larger fluctuations enhance the relaxation of protons. This is called proton-electron dipole-dipole proton relaxation enhancement (PRE). The strength of the field of a dipole decreases as the third power of the distance from the point of measurement to the dipole, and the strength of a mutual dipole-dipole interaction is proportional to the product of the two dipole fields. Hence, a dipole-dipole interaction decreases as the sixth power of the distance between the dipoles. This means that a water proton must approach within 3 angstroms (Å) of an unpaired electron for the dipole-dipole interaction to take place.

### SELECTIVE T2 RELAXATION ENHANCEMENT OWING TO HETEROGENEITY

In addition, if a paramagnetic substance is heterogeneously (nonuniformly) distributed in the volume of tissue being examined and water protons cannot come within 3 Å of the unpaired electrons, selective T2 relaxation enhancement is produced. This is in contrast to proton-electron dipole-dipole proton relaxation enhancement (PRE) which causes both T1 and T2 PRE.

The precession rate (Larmor frequency) of water protons is proportional to the local field strength, which in turn, varies with the local magnetic susceptibility. A heterogeneously distributed paramagnetic substance causes variations in local magnetic susceptibility from point to point. Following the initial 90° pulse of a spin-echo sequence phase differences develop among the precessing protons that are normally refocussed by the ensuing 180° pulses. The phase spread cannot be refocussed by the spin-echo pulse sequence, however, if the water protons diffuse to regions of

different field strengths during the pulse sequence. Thus, water protons diffusing through regions of varying field strengths due to the heterogeneous distribution of a paramagnetic substance will lose their transverse phase coherence faster; i.e., have a shorter T2 than they would in a completely homogeneous medium.

With spin-echo techniques, the T2 decreases with increase in the interecho interval (the time between 180° pulses) because there is more time for water protons to diffuse to regions of greater field difference between two consecutive echos. The effect of this T2 PRE mechanism increases as the square of the magnitude of the applied magnetic field and as the square of the variation in magnetic susceptibility. The effect of the proton-electron dipole-dipole PRE mechanism, on the other hand, varies little or decreases with increasing field strength.

## Structural Characteristics of Hemoglobin Degradation Products That Affect Relaxation Rates

Oxyhemoglobin contains iron in the ferrous ($Fe^{+2}$) state but is not paramagnetic. Deoxyhemoglobin contains iron in the ferrous ($Fe^{+2}$) state with four unpaired electrons and is paramagnetic. These unpaired electrons, however, are shielded from direct dipole-dipole interaction with water protons.

The iron of methemoglobin is in the ferric state ($Fe^{+3}$), has five unpaired electrons and is paramagnetic. In this case, the unpaired electrons cause proton relaxation enhancement by the dipole-dipole interaction (shorter T1 and T2).

Ferritin and hemosiderin have a similar structure with a core containing, on the average, 2,000 iron atoms in the $Fe^{+3}$ state (5 unpaired electrons per iron atom). The iron cores are 50–70 Å in diameter and are surrounded by a protein shell with an outer diameter of about 120 Å. Most of the unpaired electrons of the iron in ferritin are shielded from direct dipole-dipole interactions with water protons. The iron cores are single-domain crystals of FeOOH (ferric hydroxyoxide) and are superparamagnetic; i.e., all the unpaired electron spins of the iron core stay parallel to (remained aligned with) each other. In effect, each ferritin and hemosiderin core acts as a magnet which is always oriented in the direction of the applied magnetic field, and whose strength increases with the field strength.

## Effects of Relaxation Rate Changes on Signal Intensities of Hemorrhages *(3)*

### ACUTE HEMORRHAGE

In acute hemorrhage, depending on the pH and $pO_2$, the hemoglobin loses its oxygen, becoming deoxyhemoglobin (Hb) which is paramagnetic because it has 4 unpaired electrons. In the physiological range, a lowering of the pH shifts the oxyhemoglobin dissociation curve to the right; i.e. more desaturated hemoglobin (Bohr effect). Increasing the $CO_2$ (at constant pH) also lowers the oxygen affinity. Its unpaired electrons are inaccessible for dipole-dipole interaction with water protons, but intracellular deoxyhemoglobin (Hb IRBC) has heterogeneous magnetic susceptibility. When an external magnetic field is applied, the higher susceptibility inside the red cell (RBC) containing the deoxyhemoglobin results in field gradients inside and outside the cell (across the cell membrane) (Figure 2). Although the spin-echo sequence will correct for static field inhomogeneities, it will not completely correct

for the effects of water proton diffusion across field gradients (Figure 3). On spin-echo sequences, the T2 relaxation rate (1/T2) due to intracellular deoxyhemoglobin increases as the square of the magnetic field strength and increases with lengthening of the interecho interval (Figures 4–8). The increased T2 relaxation rate results in a decrease in the signal intensity of a hemorrhage on T2 weighted images.

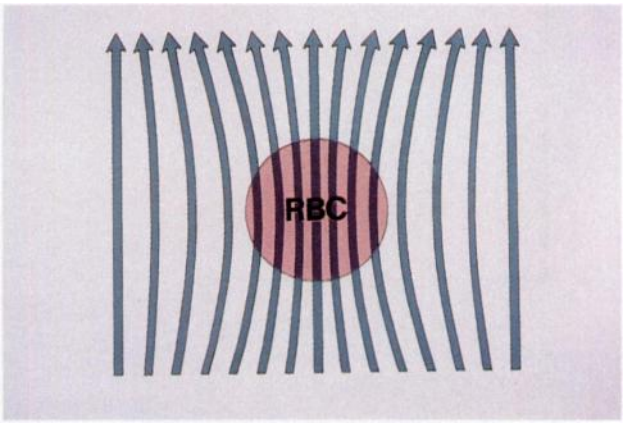



**Figure 2**
Distortion of the magnetic field lines by the difference in magnetic susceptibility between intracellular deoxyhemoglobin and extracellular plasma.

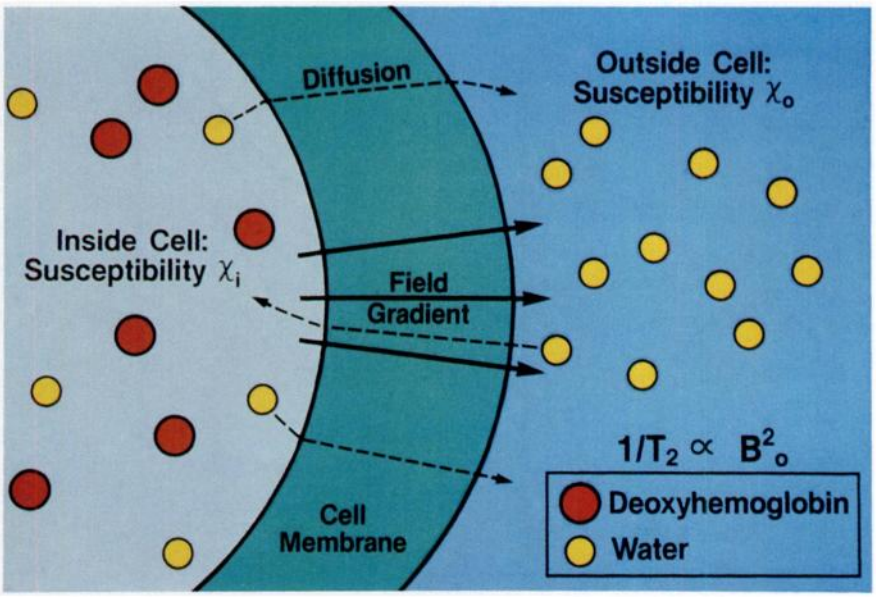



**Figure 3**
Diffusion of water across the cell membrane to regions of different magnetic susceptibility and therefore to regions of different augmented local field strengths.

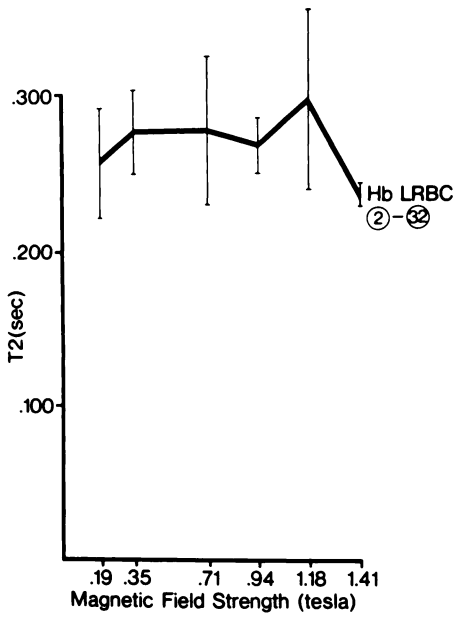



**Figure 4**
Variation of T2 of deoxyhemoglobin lysate as a function of magnetic field strength with interecho intervals from 2 msec to 32 msec. Hb LRBC = deoxyhemoglobin, lysed red blood cells

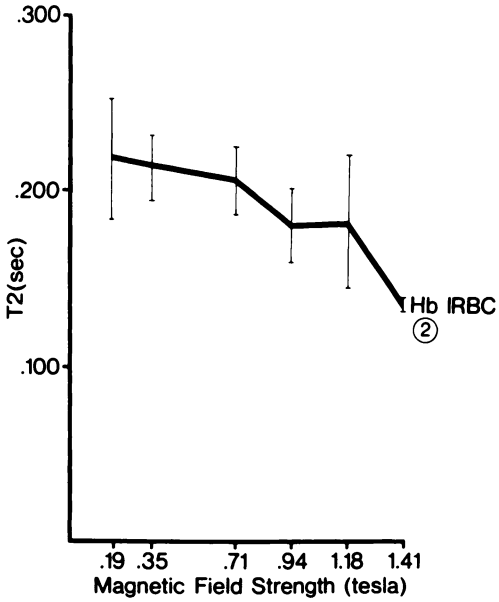



**Figure 5**
Variation of the T2 of intracellular deoxyhemoglobin as a function of field strength with an interecho interval of 2 msec. Hb IRBC = deoxyhemoglobin, intact red blood cells

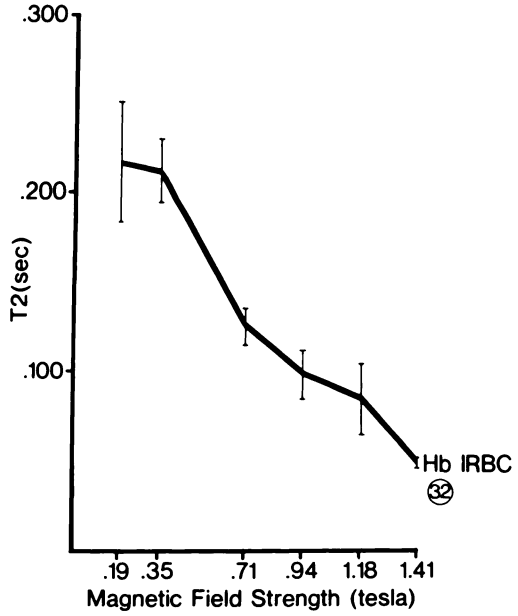



**Figure 6**
Variation of the T2 of intracellular deoxyhemoglobin as a function of field strength with an interecho interval of 32 msec. Hb IRBC = deoxyhemoglobin, intact red blood cells

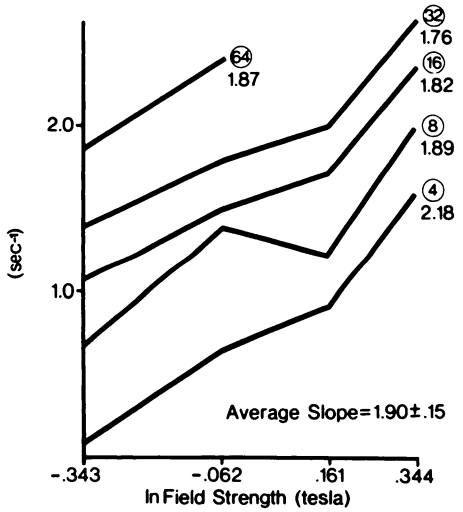



**Figure 7**
Variation with field strength of the T2 relaxation rate (1/T2) of intracellular deoxyhemoglobin owing to intracellular deoxyhemoglobin's paramagnetic susceptibility. The slope of the individual plot in this ln-ln graph indicates the exponent of the relationship between the relaxation rate and field strength. The circled numbers are the interecho intervals in msec and the number under each of them is the average slope of the curve. The average of all the curves is indicated at the bottom.

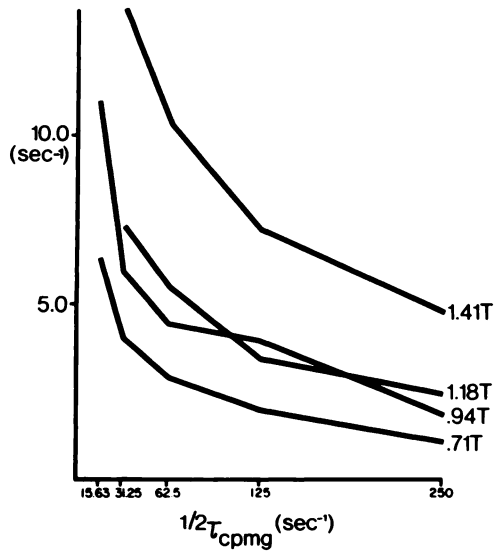



**Figure 8**
Variation of the T2 relaxation rate (1/T2) of intracellular deoxyhemoglobin as a function of the echo rate ($\frac{1}{2}\tau_{cpmg}$); i.e., the inverse of the interecho interval ($2\tau_{cpmg}$). Note the marked increase in T2 relaxation rate with long interecho intervals (short $\frac{1}{2}\tau_{cpmg}$).

## SUBACUTE HEMORRHAGE

Methemoglobin (MHb) is paramagnetic because it has 5 unpaired electrons. These electrons are accessible to water protons for dipole-dipole interactions which shorten both T1 and T2. This interaction is not significantly affected by field strength or cell integrity. In the MRI of dilute solutions of methemoglobin, the T1 shortening is more important than the T2 shortening. Figures 9–11 depict the variations in the T1 of plasma and various states of hemoglobin with field strength. Intracellular methemoglobin (MHb IRBC) also possesses heterogeneous magnetic susceptibility. From equation 1 (page 429), its magnetic susceptibility is proportional to (5) × (5 + 2), and the magnetic susceptibility of deoxyhemoglobin is proportional to (4) × (4 + 2). Also from page 429, the T2 relaxation rate of a paramagnetic substance varies as the square of its magnetic susceptibility. Hence, on spin echo sequences, the T2 relaxation rate of methemoglobin is 2.13 times that of intracellular deoxyhemoglobin.

$$[(5)(5 + 2)/(4)(4 + 2)]^2 = (35/24)^2 = 2.13$$

It also increases as the square of the magnetic field strength and with interecho interval lengthening (Figures 12–15). On gradient echo sequences, however, the 1/T2* of methemoglobin will be only 1.46 times that of intracellular deoxyhemoglobin.

$$[(5)(5 + 2)/(4)(4 + 2)] = (35/24) = 1.46$$

Table I summarizes the relationships responsible for the MR appearance of acute and subacute hematomas.

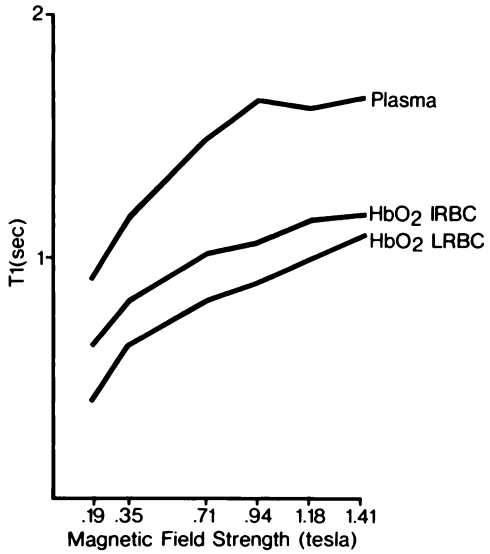



**Figure 9**
Variation of the T1 relaxation times of plasma, intracellular oxyhemoglobin and oxyhemoglobin lysate as a function of field strength. $HbO_2$ IRBC = oxyhemoglobin, intact red blood cells $HbO_2$ LRBC = oxyhemoglobin, lysed red blood cells

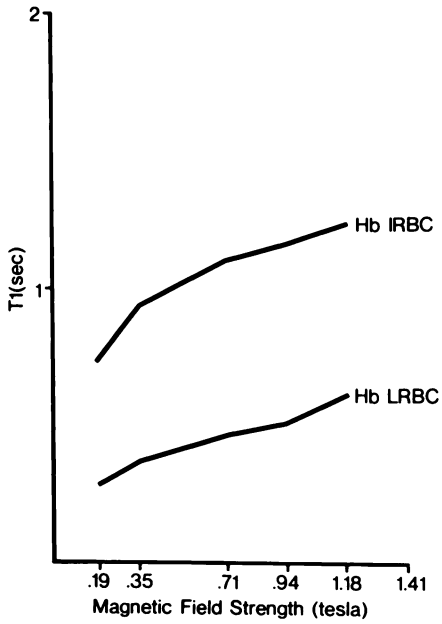
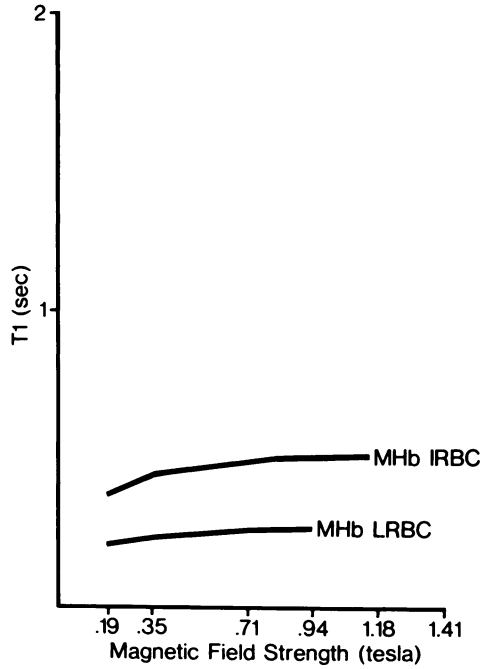



**Figure 10**
Variation of the T1 relaxation times of intracellular deoxyhemoglobin and deoxyhemoglobin lysate as a function of field strength. Hb IRBC = deoxyhemoglobin, intact red blood cells Hb LRBC = deoxyhemoglobin, lysed red blood cells

**Figure 11**
Variation of the T1 relaxation times of intracellular methemoglobin and methemoglobin lysate as a function of field strength. MHb IRBC = methemoglobin, intact red blood cells MHb LRBC = methemoglobin, lysed red blood cells



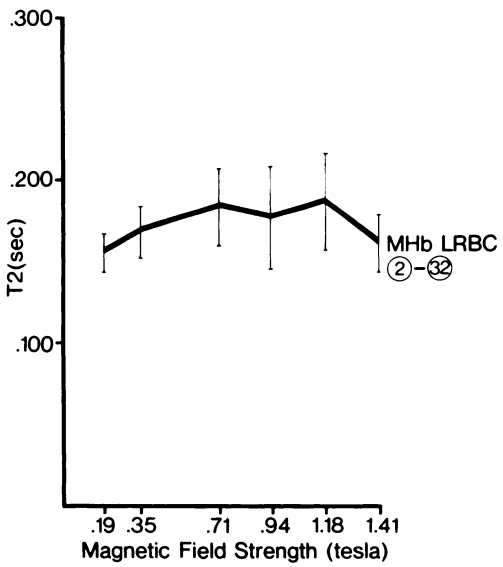



**Figure 12**
Variation of the T2 relaxation of methemoglobin lysate as a function of field strength. There was no change in relaxation time as a function of interecho intervals from 2 msec–32 msec. MHb LRBC = methemoglobin, lysed red blood cells

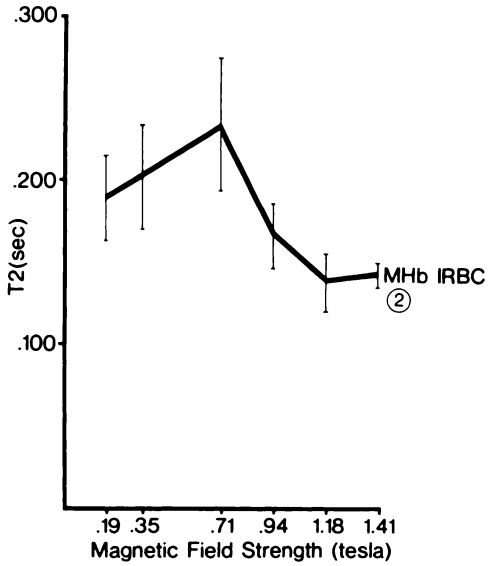



**Figure 13**
Variation of the T2 relaxation time of intracellular methemoglobin as a function of field strength at an interecho interval of 2 msec. MHb IRBC = methemoglobin, intact red blood cells

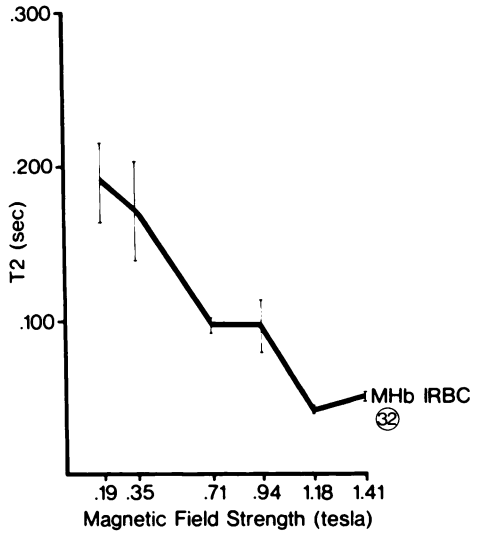



**Figure 14**
Variation of the T2 relaxation time of intracellular methemoglobin as a function of field strength at an interecho interval of 32 msec. MHb IRBC = methemoglobin, intact red blood cells

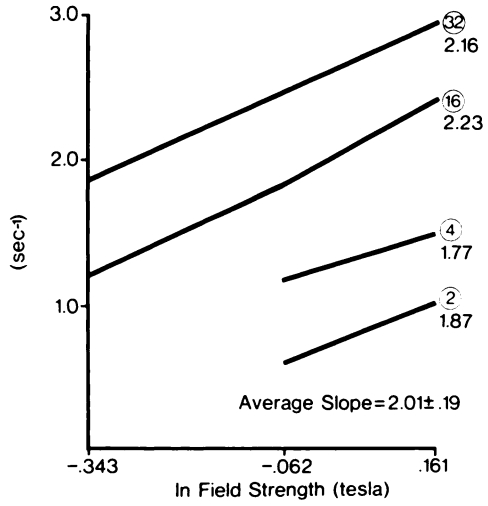



**Figure 15**
Ln-ln graph of the T2 relaxation rate (1/T2) of intracellular methemoglobin due to its paramagnetism as a function of field strength. The interecho interval of each curve in msec is circled. The number below the interecho interval represents the slope of each curve. The quadratic relation is indicated by the average slope of 2.

# TABLE I

$T2\ PRE \propto (Hct)(100 - Hct)\{(Hb\ IRBC) + 35/24(MHb\ IRBC) - (Hb\ LRBC) - 35/24(MHb\ LRBC)\}^2 B_0^2$

$T2' PRE \propto (Hct)(100 - Hct)\{(Hb\ IRBC) + 35/24(MHb\ IRBC) - (Hb\ LRBC) - 35/24(Hb\ LRBC)\}B_0$

$PEDD\ PRE \propto \{(MHb\ IRBC) + (MHb\ LRBC)\}$

$(PD_w - PD_h) \propto \{(HbO_2\ IRBC) + (Hb\ IRBC) + (MHb\ IRBC) + (HbO_2\ LRBC) + (Hb\ LRBC) + (MHb\ LRBC)\}$

| | |
|---|---|
| $\propto$ | Approximately proportional to |
| T2 PRE | 1/T2 on spin-echo MR due to susceptibility heterogeneity |
| T2' PRE | 1/T2' on gradient-echo MR due to susceptibility heterogeneity |
| PEDD PRE | 1/T1 and 1/T2 due to proton-electron dipole-dipole proton relaxation enhancement |
| Hct | Hematocrit |
| $B_0$ | Strength of magnetic field |
| $(HbO_2\ IRBC)$ | Intracellular oxyhemoglobin |
| $(HbO_2\ LRBC)$ | Extracellular oxyhemoglobin |
| (Hb IRBC) | Intracellular deoxyhemoglobin |
| (Hb LRBC) | Extracellular deoxyhemoglobin |
| (MHb IRBC) | Intracellular methemoglobin |
| (MHb LRBC) | Extracellular (free) methemoglobin |
| $PD_w$ | Proton density of pure water |
| $PD_h$ | Proton density of hematoma |

## CHRONIC HEMORRHAGE *(1,2)*

Hemosiderin and ferritin are very closely related chemically. They are the characteristic components of chronic hematomas. The more abundant hemosiderin is insoluble and is found mostly in the lysosomes of reactive macrophages in the brain parenchyma surrounding a hemorrhage. Ferritin is water soluble and homogeneous solutions of ferritin have a significant 1/T2 (rate of T2 relaxation) that increases almost as the square of the field strength but does not vary with spin-echo interecho interval (between 2–32 msec) (Figure 16). This appears to be due to the superparamagnetic susceptibility of ferritin resulting in field gradients near the ferritin macromolecule. The 1/T2 of hemosiderin deposits containing an equivalent amount of iron is 5 times greater. Not only does the T2 relaxation rate of hemosiderin increase quadratically with field strength, it also increases with lengthening of the spin-echo interecho interval (Figures 17–19). The heterogeneous distribution of hemosiderin was modeled with a heterogeneous distribution of ferritin obtained by suspending intact oxygenated red cells (nonparamagnetic) in an equal volume of ferritin solution thus creating a field gradient across the red cell membrane. The additional 1/T2 owing to the heterogeneous distribution of ferritin was about 4 times that attributable to the paramagnetic properties of ferritin itself, at 1.4 T with long spin-echo interecho intervals (Figures 20–22). This confirms that the dominant contributor to the T2 relaxation rate of hemosiderin deposits is the heterogeneous distribution of hemosiderin. Figure 23 summarizes the properties of various constituents of hemorrhage.

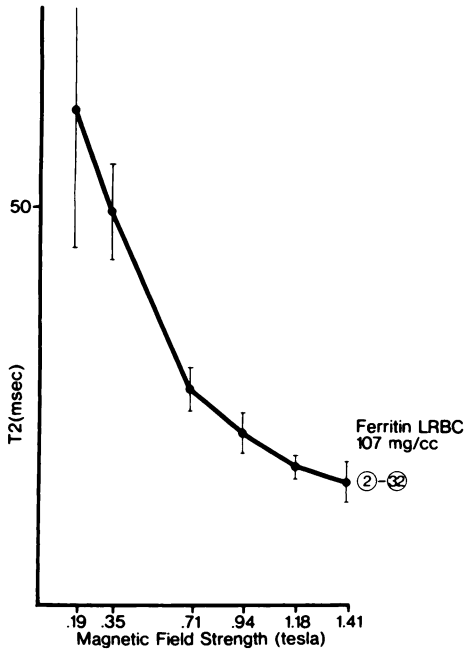



**Figure 16**
Variation of the T2 relaxation time of a ferritin red cell lysate as a function of field strength. The T2 relaxation time was unaffected by the intercho interval at interecho intervals between 2 msec and 32 msec. LRBC = lysed red blood cells

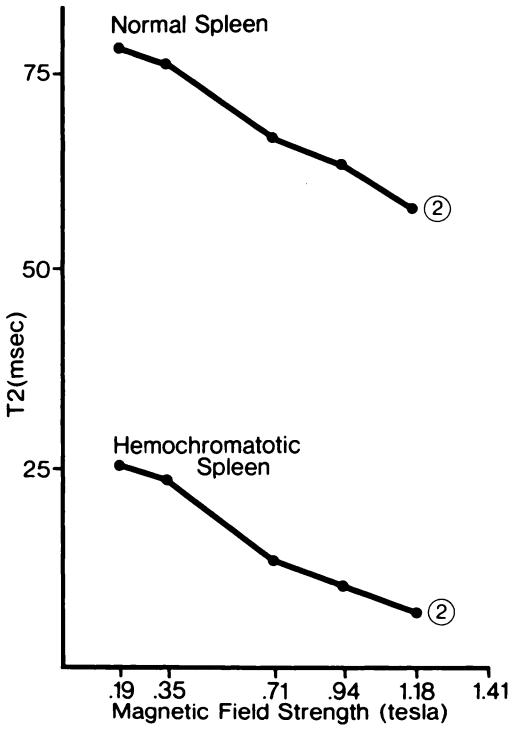



**Figure 17**
Variation of the T2 relaxation times of a normal spleen sample (0.52 mg Fe/g) and of a hemochromatotic spleen sample (10.6 mg Fe/g) as functions of field strength. The interecho interval was 2 msec.

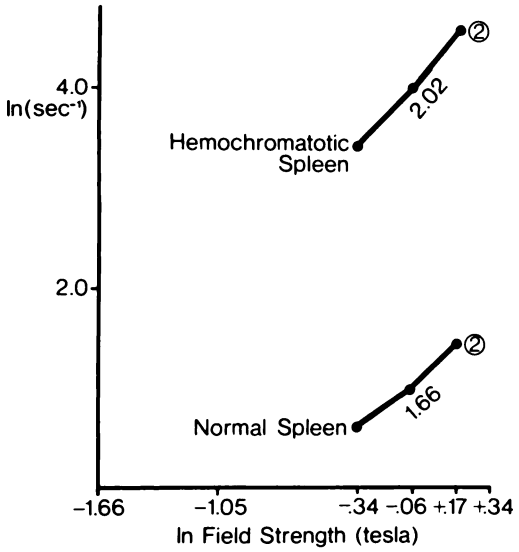



**Figure 18**
Ln-ln graph of the field strength dependent relaxation rate versus field strength for normal and hemochromatotic spleen samples. The interecho interval was 2 msec.

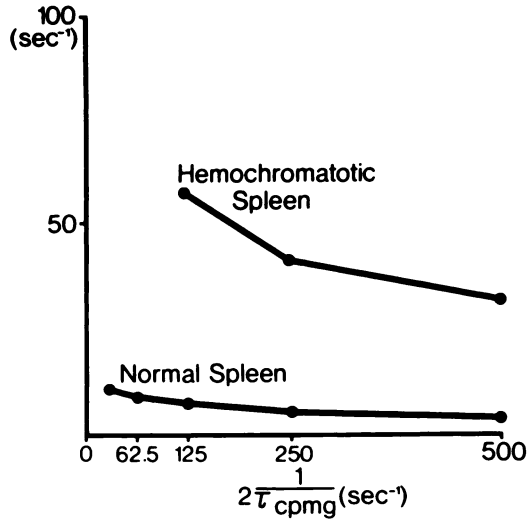
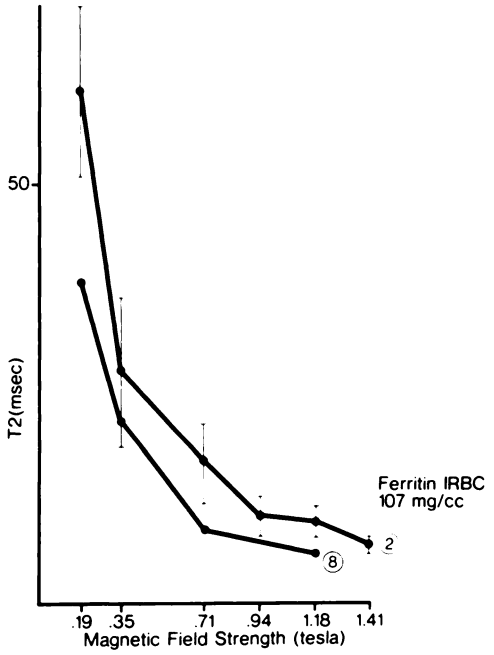



**Figure 19**
Variation of the T2 relaxation rate (1/T2) of a normal spleen sample as a function of echo-rate ($\frac{1}{2\tau_{cpmg}}$) at 1.4 T and of a hemochromatotic spleen sample at 0.71 T.

**Figure 20**
Variation of the T2 relaxation time of a ferritin red cell (IRBC) suspension as a function of field strength. The circled numbers identify the plots at spin-echo intercho intervals of 2 msec and 8 msec. IRBC = intact red blood cells



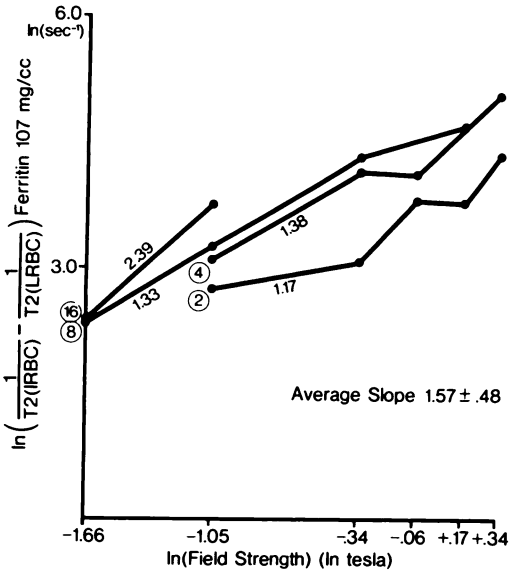



**Figure 21**
Ln-ln graph of the variation in the T2 relaxation rates of ferritin (1/T2) owing to the heterogeneity in susceptibility caused by the suspension of red cells in the ferritin as a function of the field strength. The interecho intervals in msec are indicated as circled numbers. The slope of each curve is indicated adjacent to the plot. The average slope is consistent with a quadratic relationship between field strength and relaxation rate (1/T2). IRBC = intact red blood cells LRBC = lysed red blood cells

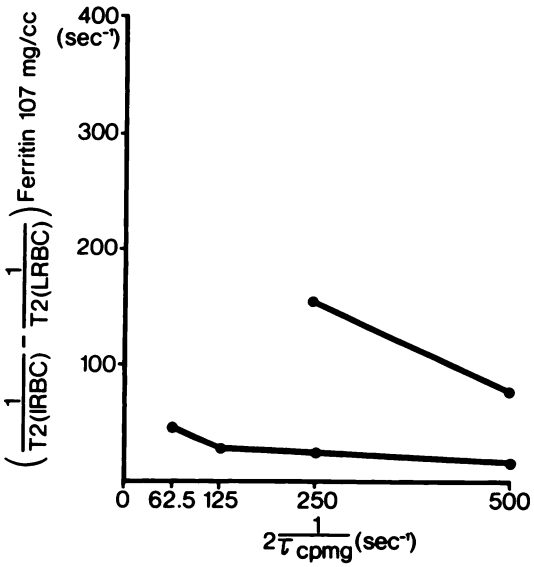



**Figure 22**
Variation of the T2 relaxation rate (1/T2) of ferritin owing to the heterogeneity of susceptibility caused by the suspension of red cells in ferritin as a function of the echo-rate ($\frac{1}{2}\tau_{cpmg}$) at 0.35 T (lower plot) and 1.4 T. IRBC = intact red blood cells LRBC = lysed red blood cells $2\tau_{cpmg}$ = spin-echo interecho interval

**Figure 23**
Summarizes the MR properties of the various constituents of hemorrhage. T1WI, Proton Density WI and T2WI refer to T1, Proton Density and T2 weighted images respectively.

| Molecule | Iron Form | # Unpaired Electrons | Water Soluble | PEDD PRE | Distribution | T2 PRE | Proton Density | T1WI | Proton Density WI | T2WI |
|---|---|---|---|---|---|---|---|---|---|---|
| Oxyhemoglobin | $Fe^{+2}$ | 1 | + | − | IRBC | − | −− | −− | −− | −− |
| ↑Sensitivity to $pO_2$ & pH | | | | | LRBC | − | −− | −− | −− | −− |
| Deoxyhemoglobin | $Fe^{+2}$ | 4 | + | − | IRBC | + | −− | −− | −− | ↓ |
| | | | | | LRBC | − | −− | −− | −− | −− |
| Methemoglobin | $Fe^{+3}$ | 5 | + | + | IRBC | + | −− | ↑ | −− | ↓ |
| | | | | | Concentrated LRBC | − | −− | ↑ | −− | ↓ |
| | | | | | Dilute LRBC | − | ↑ | ↑↑ | ↑↑ | ↑↑ |
| Ferritin | $Fe^{+3}$ | ~10,000 | + | − | Intracellular | + to ++ | −− | −− | −− | ↓ |
| Hemosiderin | $Fe^{+3}$ | ~10,000 | − | − | Intralysosomal | + to ++ | −− | −−or ↓ | ↓ | ↓ |

Arrows indicate increased (↑) or decreased (↓) signal intensity. Size of arrow indicates magnitude of the effect.

## Gradient Echo Techniques in the MR Imaging of Hemorrhage

The spin-echo technique has been used to overcome static field and chemical shift inhomogeneities; but the high field uniformities achieved in modern MR units permit us to discard the refocussing 180° pulses in a spin-echo sequence. The introduction of gradient-echo techniques has exciting implications for the MRI of hematomas *(4)*. With these techniques, it is possible to obtain much greater sensitivity to field inhomogeneities that are caused by the heterogeneity of magnetic susceptibility intrinsic to the tissues of the patient. Gradient echo techniques are sensitive to heterogeneity over the dimensions of an image voxel (approximately 1 mm) rather than the distance diffused by water between echoes (approximately 0.01 mm). This increased sensitivity is manifested by one's ability to observe magnetic susceptibility differences at lower field strengths and by one's ability to detect heterogeneous susceptibility over much larger distances; e.g., inhomogeneous clotting. There will be no significant change in apparent $T2^*$ with changes in interecho interval, and boundaries between regions of different magnetic susceptibility or chemical shift will appear to have shortened $T2^*$. The boundary between deoxyhemoglobin or methemoglobin, whether intracellular or extracellular, and the surrounding parenchyma will appear hypointense relative to normal white matter on T2 images, mimicking the hypointensity of hemosiderin deposits. This may cause some confusion when evaluating hemorrhagic tumors, which usually do not have complete hypointense rims on spin-echo sequences. Of course, similar marginal hypointensity will occur between fat and other tissues and perhaps between melanotic melanomas and surrounding tissues and between air or dense bone and other tissues. Thus, the marginal hypointensity on gradient echo imaging is not as specific as on spin echo sequences.

## Summary

The sequential degradation of hemoglobin in an evolving hemorrhage has been reviewed. Physical mechanisms of proton relaxation enhancement that contribute to the clinical MR appearances of hemorrhage have been described, and the dependence of relaxation rates on field strength and interecho interval in spin-echo imaging techniques has been defined.

## References

1. Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT: Intracranial hematomas: Imaging by high-field MR. Radiology 1985; 157:87–93.
2. Gomori JM, Grossman RI: Mechanisms responsible for the MR appearance and evolution of intracranial hemorrhage. (abstr.) Radiology 1986; 161(P):364.
3. Gomori JM, Grossman RI, Yu Ip C, Asakura T: Dependence of NMR relaxation times of blood on field strength, oxidation state, and cell integrity. J Comput Assist Tomogr 1987; 11:684–690.
4. Edelman RR, Johnson K, Buxton R, et al. MR of hemorrhage: a new approach. AJNR 1986; 7:751–756.