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Conception of the First Magnetic Resonance Imaging Contrast Agents: A Brief History

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Summary: About 20 years ago, a technological innovation process started that eventually led to the affirmation of magnetic resonance imaging (MRI) contrast agents, which are used today in about 25% of all MRI procedures, as medical diagnostic tools. The process began with exploration of various technical possibilities and the conception in the years 1981 to 1982 of two types of agents (soluble paramagnetic chelates and protection colloid-stabilized colloidal particle solutions of magnetite) that eventually found embodiments in commercially available products. The pioneering products that eventually reached the market were gadopentetate dimeglumine (Magnevist®, Schering AG) and the ferumoxides (Endorem®, Guerbet SA; or Ferridex®, Berlex Laboratories Inc.). The history of the conception phase of the technology is reconstructed here, focusing on the social dynamics rather than on technological aspects. In the period 1981 to 1982, a number of independent inventors from industry and academia conceived of water-soluble paramagnetic chelates and protection colloid-stabilized colloidal solutions of small particles of magnetite, both of acceptable tolerability, as contrast agents for MRI. Priorities on patents conditioned the further course of events. The analyzed history helps in understanding the typical roles of different institutions in technological innovation. The foundation of MRI contrast agent technology in basic science clearly was laid in academia. During the conception of practical products, industry assumed a dominant role. Beginning with the radiological evaluation of candidate products, the collaboration between industry and academia became essential. **Key Words:** Magnetic resonance imaging—Contrast agents—History.

About 20 years ago, magnetic resonance imaging (MRI) contrast agents initiated a process of technological innovation, as defined by Schumpeter (1). Such innovation typically arises in different phases: conception, development, and affirmation. A short history of the conception phase of MRI contrast agents is presented here and is aimed more at elucidating the not-so-visible social dynamics of technological innovation, specifically for MRI contrast agents, rather than the technological details. The latter aspects have been described in detail by others (2). The speed with which the field progressed during the critical period caused presentations at congresses and published patent applications to become a more important communication vehicle than full publications in journals. This is taken into account in the present analysis.

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MRI was conceived in 1971. The basic concepts and experiments published by Damadian (3) allowed him to obtain within the 1-year grace period after his publication, on March 17, 1972, an eventually successful U.S. patent application (4). In 1971, Paul C. Lauterbur, as interim president of a company involved in nuclear magnetic resonance (NMR) equipment manufacturing, had the occasion to watch the physiological chemistry graduate student Leon A. Saryan in the laboratory of Donald P. Hollis at Johns Hopkins University perform experiments similar to the earlier experiments of Damadian (5). Inspired by what he saw, on September 2, 1971, Lauterbur produced his first witnessed page of a description of MRI. Unfortunately for Lauterbur's own attempt at patenting in the spring of 1972, Damadian had the earlier conception date and Lauterbur's proposed projection reconstruction was not novel. However, a new technology almost never is based on a single invention. Indeed, many technical breakthroughs and inventions still were needed before practical MRI equipment became a reality. Lauterbur made numer-

ous crucial contributions to the emergence of MRI, beginning with the introduction of linear magnetic field gradients in combination with projection reconstruction into the first apparatus that actually was able to produce proton images of two glass capillaries filled with water in a bath of deuterium oxide (6).

Further rapid and substantial progress in the design of equipment boded well for an important clinical role of the new imaging modality. Image contrast was strong and could be amply manipulated by varying the image acquisition parameters. This nurtured the widely held expectation that, unlike in the field of X-ray based imaging, contrast agents would find no place in MRI. Things turned out differently, and today worldwide 25% of all MRI examinations are performed with contrast agents.

Of fundamental importance for the conception of MRI contrast agents was the observation of differential water proton relaxation rates in various tissue compartments. The biophysical origin of the differences in relaxation rates had already become a hot research topic in the 1960s and 1970s. Since the seminal studies of Felix Bloch in 1946 (7), the mechanisms by which paramagnetic ions accelerated the magnetic relaxation of water protons were studied and highly satisfactory explanatory theories became available (for review, see reference 8). It is no wonder the question arose: What contribution do paramagnetic ions naturally present make to relaxation rates in vivo (for review see reference 9)?

In parallel with the investigation of these questions, NMR spectroscopists explored how the addition of paramagnetic ions to aqueous solutions could be used to obtain information on the molecular structure of solutes and on enzymatic mechanisms. In this latter context, the paramagnetic manganese Mn-(II) ion, which can substitute for the nonparamagnetic magnesium Mg ion in most Mg-dependent enzymatic reactions, gained recognition as a mechanistic probe (10). Lanthanide ions, gadolinium Gd-(III) ion in particular, were found interesting because they bind at sites on proteins where the uranyl ion used in protein crystallography localizes, and, through their magnetic properties, allow measurement of certain distances on enzymes in solution (11).

From these studies, it was just a small, but no less crucial, step to explore the potential of paramagnetic ions in deliberately altering in vivo MR parameters, particularly relaxation rates. In April 1978, the laboratories of Donald P. Hollis at Johns Hopkins University (12) and Paul C. Lauterbur at the State University of New York at Stony Brook (13) both suggested such an application. The latter rapidly followed-up with an experimental demonstration of the principle (14). An Mn-(II)-chloride solution at a dose of 0.1 mmol/kg body weight was administered into the left ventricle of a mongrel dog, whose left anterior descending coronary artery had been clamped 60 min before. The longitudinal relaxation rates (1/T1) in pieces of heart excised 30 min later correlated well with their Mn content, and both delineated well the boundary between infarcted and normal tissue. Although true imaging would have to wait until 1981, when Goldman et al. (15,16) performed similar studies, there was no doubt in Lauterbur's mind that once MRI equipment was improved, the observed differences in relaxation rates would translate into visible artificially enhanced contrast between the two tissue zones on images.

Mn-(II) ion was chosen for the studies because of its long-known pronounced effect on water proton relaxation rates and its fairly low toxicity. Moreover, there was considerable knowledge about its excretion and biodistribution, including entry into myocardial muscle cells. Although increased relaxation rates in blood plasma after administration of Mn salt had been observed (14), the thrust of the work of Lauterbur's group focused on differentiating infarcted from normal myocardium. Even if chelation of Mn-(II) ion would have been discussed within the group, it would not have been pursued, because in the given context it only would risk reducing the intended cellular uptake.

In the late 1970s, pharmaceutical companies involved in the X-ray contrast agent field were still heavily involved with the new generation of nonionic and ionic dimeric iodinated contrast agents. Even when MRI was examined thoroughly, a number of these companies saw the new imaging modality as only a distant future possibility. For example, at Bracco Industria Chimica SpA in Milan, Italy, the possible utility of MRI contrast agents was analyzed in collaboration with the Italian imaging equipment distributor Ansaldo SpA and with the help of a consulting firm, which visited university centers performing advanced MRI research (University of Aberdeen; Hammersmith Hospital, London) and radiological equipment manufacturers in Europe and Japan. Given the conclusion that contrast agents were superfluous in MRI, no research activities were initiated until much later. Similar events occurred in some competing contrast agent companies, but there were exceptions.

In June 1980, two individuals from the medical division of Siemens AG, which was involved in the development of MRI equipment, visited Schering AG in Berlin, Germany, a company strongly involved in the X-ray contrast area. The principles of MRI were presented. The widely held opinion was reiterated that the multiplicity of variable image acquisition parameters, which allow differential manipulation of signal intensity of various tissues and thus intrinsic image contrast in MRI, would make contrast

agents superfluous. Despite the prevailing skepticism, the possibility of future collaboration on contrast agents was left open, and at Schering AG the issue of how relaxation times could be influenced was discussed in presentations by Douwe Rosenberg and Georg-Alexander Hoyer in early 1981. Knowledge about the paramagnetic ion effects mentioned earlier was transmitted; in particular, copper, manganese, and gadolinium ions were mentioned as paramagnetic ions capable of predominantly shortening T1 of water. Ulrich Speck, the director of contrast agent research, charged Hanns-Joachim Weinmann with a study of the suitability of selected compounds for influencing MRI in animals, using experimental equipment at Siemens AG in Erlangen, Germany.

In X-ray contrast agent research, for which Weinmann had originally been hired, chemically altering contrast-producing compounds so as to reduce their toxicity was always one of the primary concerns. Now also in the case of MRI, the issue became how to detoxify paramagnetic metal ions. There existed much experience with such detoxification. Even in the preparation of X-ray contrast agents, metal ions with elevated X-ray absorption had been used and were detoxified by chelation. Sodium thorium dicitrate, a chelate, at one time had been commercialized as pyelographic contrast agent (17) ("Thorium Solution," The Hynson, Westcott & Dunning Pharmaceutical Laboratory Inc., Baltimore, MD, U.S.A.). Pb-(II)-EDTA disodium (18) and Bi-(III)-DTPA disodium (19) had been explored as intravenous agents. Furthermore, it was known that chelation of paramagnetic ions, e.g., Gd-(III) ion with EGTA, did not completely abolish the relaxation enhancement of the free ion, and, in the case of macromolecular proteinaceous chelating agents, the relaxation effects even could be accentuated (11). Thus, for reasons of solubility under physiological conditions and in the hopes of finding well-tolerated compounds with sufficiently preserved relaxation-enhancement properties, the chemistry department at Schering AG was asked to prepare suitable paramagnetic chelates. Heinz Gries and Douwy Rosenberg chose to prepare first well-known salts of Mn-(II)-EDTA, Gd-EDTA, and Mn-(II) citrate, which they passed to Weinmann for initial imaging studies. Mn-(II)-EDTA disodium was well tolerated. Gd-EDTA sodium showed no improvement in intravenous acute toxicity over $GdCl_3$, but it had better neural tolerability. Together with the better water solubility, these observations rendered the EDTA chelates plausible candidates for contrast media.

The first imaging studies of compound solutions in glass containers were performed under the watchful eye of Weinmann on May 19, 1981, at Siemens AG in Erlangen. With great astonishment, decreased signal intensity with respect to water was observed, which was the opposite of what had been expected. In rabbits, intravenous injection of solutions of the various compounds followed by MRI produced confusing results, epitomized by the case of $GdCl_3$. In live animals, no significant overall signal intensity increase was noted, whereas after killing the animal the liver stood out with clearly enhanced intensity. In organs isolated from the animals, Gd could be detected. To understand this finding, we need to remember that, at the time, long signal acquisition times were needed. Even then, spatial resolution was poor, especially for imaging a small animal in a large magnet.

The available theory of relaxation effects of paramagnetic ions predicted that at high enough concentrations, T2 effects would overwhelm T1 effects and lead to signal abolition with the image acquisition parameters used at the time. Weinmann realized this, and the first positive results after injection of lower doses showed that he was on the right track, although the images remained murky.

Tolerabilities of the complexes studied up to that time still left ample room for improvement. Thus, Weinmann, in collaboration with the chemists Gries and Rosenberg, identified additional already known and novel chelates of potential suitability. In particular, Gd-DTPA salt was singled out. Formation of this complex in solution (20), the formation constant for the 1:1 complex (21), its infrared spectrum as a solid (22), and its use as a relaxation agent for ^{15}N-NMR in aqueous solution (23) had already been described in the literature. At the time, DTPA was one of the chelating agents on the shelf of many biochemists and pharmacologists and, as described earlier, had already been explored for the detoxification and solubilization of bismuth as an X-ray contrast agent. It also had been used to carry radioisotopes into the brain for the detection of blood–brain barrier breakdown in tumors (24). Thus, analogous use in MRI was conceivable, if sufficiently elevated concentrations could be achieved. However, nobody could know in advance whether the product would be well tolerated and have satisfactory relaxation properties.

Early demonstration of MRI signal enhancement by some prototypical paramagnetic chelates whose toxicity characteristics fell into a reasonable range allowed application on July 24, 1981 for a first patent covering the composition of matter for use as MRI contrast agents (25). The application included the preparation of Gd-DTPA as an example, even though neither toxicity nor MRI studies had yet been performed. It is fascinating to realize that only about 1 month before, on June 17, a manuscript was submitted for publication, which gave a detailed description of the synthesis of Gd-DTPA and its use as a water-soluble relaxation agent for ^{13}C-NMR studies (26). As in

so many other cases, after the fact, the invention of paramagnetic chelates as MRI contrast agents seemed obvious and a logical next step of ongoing investigations, yet nobody put all the elements together correctly. This patent, which withstood deep-probing adversary examination, after being extended to many countries, was published and granted, and it laid the cornerstone of all future developments of paramagnetic complexes as MRI contrast agents.

In early August 1981, the tolerability of Gd-DTPA salt was studied by routine methods in the Schering laboratories. In parallel, Weinmann performed systematic studies of the effects of paramagnetic chelates at various concentrations on relaxation times, using the facilities of the Physics Department of the Freie Universität, Berlin, Germany. It turned out that Gd-DTPA salt was not only extremely well tolerated by animals and was highly soluble, it also preserved good relaxation properties. Imaging studies at a suitable dose of Gd-DTPA salt confirmed its identification as a realistic MRI contrast agent. A new and potentially useful application of a known compound had been found. Its safety margin was surprisingly higher than what was considered excellent in the X-ray contrast agent field. Thus, the earlier patent application had indeed taught how practical injectable MRI contrast agents could be achieved.

Given the available results, Schering AG focused further efforts exclusively on Gd-DTPA salts. In new animal imaging studies at Siemens AG on May 5, 1982, Weinmann for the first time observed Gd-DTPA–dependent enhancement of tumor signal intensity in a live animal model. In the next few months, imaging experiments with solutions of Gd-DTPA salt in simple containers were performed at Royal Philips Electronics N.V. in Eindhoven, The Netherlands, and later in collaboration with Picker International Ltd. at the Hammersmith Hospital, London, United Kingdom. The physicist Leon Kaufman at the Oyster Point facility in South San Francisco, part of the University of California at San Francisco, was equipped with an MRI apparatus especially suitable for imaging small animals. Although convinced of the uselessness of contrast agents, Kaufman allowed other investigators access to his equipment, although understandably on a very limited basis. In June 1982 Weinmann obtained sufficient time to perform, with the help of Kaufman's Staff Research Associate, Tony Brito, complete dose-finding studies for intravenous Gd-DTPA salt in rats and to demonstrate the usefulness of the contrast agent in imaging inflammation. In addition, he could explore the contrast agent's utility after oral or rectal administration. Finally, he examined the properties of some compounds bearing nitroxide free radicals he had brought along. With Gd-DTPA salt, images superior to anything seen before using clinical instrumentation were obtained. At the end of the studies, Weinmann visited Robert C. Brasch in his office at the University of California at San Francisco. Brasch was a consultant to Schering AG on the mechanisms of adverse reactions to X-ray contrast media. In his own research, Brasch and a number of collaborators had pursued MRI contrast agents, using the same imaging equipment. His focus was on nitroxide free radicals as paramagnetic contrast molecules (discussed in detail later) (27). At that time, the two investigators only compared results. Brasch seemed astonished by the images Weinmann had obtained with Gd-DTPA salt. A year later, Weinmann returned to San Francisco for another round of experiments, this time collaborating with Brasch on studies with Gd-DTPA salt as well as on compounds expected to produce liver-specific MRI signal enhancement. In that year, Weinmann and Brasch, and their collaborators, jointly published some results with Gd-DTPA salt (28).

In late 1981, at some meetings, the first reports on MRI of normal and infarcted canine heart after administration of Mn-(II)-chloride were presented (15,16). There was no mention of chelates. During the first annual meeting of the Society of Magnetic Resonance in Medicine in Boston in August 1982, there were two presentations on pharmacological manipulation of MRI contrast. In the first presentation, Mendonça Dias et al. (29) presented work on manganese chloride as an intravenous contrast agent in animal imaging. EDTA was injected only after imaging to accelerate elimination of Mn (29). In the second presentation, Brasch and collaborators (27) introduced stable nitroxide free radicals as paramagnetic contrast agents (as described later). Comforted by the evidence that the use of paramagnetic chelates was not yet publicly discussed and by its own promising results, in September 1982 the management at Schering AG ordered acceleration of the research program.

With a crafty strategy of initial and subsequent intellectual property protection, the patent office of Schering AG achieved broad and long-lasting coverage of intellectual property rights, on which all similar contrast agents developed later in other companies continue to depend. It is worth emphasizing that only good coverage of intellectual property could justify the dozens of millions of dollars in clinical trial expenses needed to register commercial products and thus make the new technology widely available within reasonable times.

On February 10, 1983, the German patent application of Gries et al. (25) appeared in print. Now, for the first time, companies competing with Schering AG in the X-ray contrast agent area, and the few academics who followed the patent literature, were alerted to ongoing industrial activities on paramagnetic chelates as MRI contrast agents.

At Mallinckrodt Inc. (St. Louis, MO, U.S.A.), a company active in the area of X-ray contrast agents and in nuclear medicine diagnostic products, the publication of the patent application of Schering AG must have created disappointment and concern. In that company, Geo[rge] Brooke Hoey, the Director of Contrast Media Research, had already instituted exploratory studies on MRI contrast agents. Some pharmaceutical and pharmacological studies with a preparation of Mn-(II)-EDTA disodium salt, some of it entrapped in multilamellar liposomes, had preceded initial MRI experiments. On April 19, 1982, the company pharmaceutical chemists Mark E. Bosworth and Ronald M. Hopkins furnished a preparation "For animal studies by Dr. Wolf" (30). Indeed, the first MRI prints with astonishingly strong artificial signal contrasts in dogs are machine dated April 20, 1982 (31). The images were obtained by the radiologist Gerald L. Wolf from the University of Pennsylvania who, not yet owning MRI equipment, enjoyed the collaboration of the engineers Paul A. Bottomley and William A. Edelstein at the General Electric Inc. Corporate Research and Development facility in Schenectady, New York. On December 8, 1982, before Schering's activities became public knowledge, the same chemists delivered a Gd-DTPA disodium salt solution to Hoey for MRI studies by Wolf (32). The results were reported 3 months later (33). Thus, at Mallinckrodt Inc., research on MRI contrast agents had been initiated relatively early and was well centered, but in terms of priority it came after the efforts at Schering AG.

Independently of all this, in the fall of 1982, a group composed of Jean-Marie Caillé and Bernard Lemanceau from the Hôpital Pellegrin in Bordeaux, France, and Bruno Bonnemain from the contrast agent producer, Laboratoire Guerbet SA, Aulnay-sous-Bois, France, initiated studies on artificial MRI contrast generation. They considered contrast agents that would alter proton density, agents that could be imaged through their content in hydrogen isotopes or fluorine, and agents that modify proton magnetic resonance. In the context of the latter possibility, they identified gadolinium as the most useful element. Toward the end of the year, the first in vitro relaxation rate measurements on tissues of animals to which gadolinium chloride had been administered were presented (34,35). Due to lack of access to equipment, no imaging was performed.

Also independently of all others, in the fall of 1982, a group of researchers from the Vanderbilt University in Nashville, Tennessee, including Val M. Runge, Robert G. Stewart, Jeffrey A. Clanton, Mark M. Jones, Charles M. Lukehart, C. Leon Partain, and A. Everett James, pursued MRI contrast agents. After first studying solutions of some simple paramagnetic salts, they settled on suspensions of gadolinium oxalate for oral, and solutions of Cr-(III)-EDTA sodium for intravenous use as the most realistic MRI contrast agents. Cr-(III)-EDTA sodium was a known product of low toxicity (36) and, labeled with chromium-51, served to measure glomerular filtration rates (37). Initial in vitro measurements of T1 were performed on serially diluted suspensions and solutions of these substances. For imaging studies, they flew to the Cleveland factory of Technicare Corp., Solon, Ohio, a company involved in MRI equipment development. There, using a 0.3-T instrument, they showed contrast enhancement on T1-weighted images of kidney, ureters, and bladder of a dog after intravenous administration of Cr-(III)-EDTA sodium. The results, including the images of the enhanced bladder and kidney, were presented at the 1982 meeting of the RSNA. This was the first public presentation of results with a paramagnetic chelate as MRI contrast agent. The results appeared in print only after unfortunate delays (38,39). In the first publication (38), the authors revealed that they had made a patent disclosure to their university. Nothing came of it, because in the process of patent writing in early 1983, the investigators became aware of the much earlier patent application by Schering AG.

Also at the 1982 RSNA meeting, Brasch presented work in progress in the field of MRI contrast agents. He considered it unlikely that paramagnetic metal ions as such would ever become MRI contrast agents, but stated: "Perhaps nontoxic complexes of these ions can be developed that are rapidly excreted but retain a strong proton relaxation enhancement" (40). He gave no sign of having tried this approach yet, but he had seen some results with Gd-DTPA salts obtained by Weinmann. On April 26, 1983, a group from the University of California at San Francisco, i.e., Barry L. Engelstad, Robert C. Brasch, Robert S. Hattner, George Wesbey, and John P. Huberty, deposited a U.S. patent application covering paramagnetic chelates as MRI contrast agents. The invention was exemplified by studies with ferrioxamine B only, but the patent claims covered paramagnetic chelates widely, including Gd-DTPA salts (41). Gd-DTPA salts were studied subsequently (42). Curiously, a U.S. patent eventually was granted (41). However, in the end, the patent of Gries et al. (25) remained dominant, which implicitly recognizes the group at Schering AG as the earliest inventor of the technology of paramagnetic chelates as MRI contrast agents.

In terms of inventorship with potential economic benefits, these efforts, like those at Mallinckrodt Inc. in collaboration with the University of Pennsylvania, those at the Hôpital Pellegrin in Bordeaux in collaboration with Laboratoire Guerbet SA, those at the University of California at San Francisco, and those at Vanderbilt University, lost out to the precocious activity at Schering AG.

Such is the competitive dynamics in technological innovation. However, one may look at this issue in another way. Instead of focusing on relatively small time differences between distinct inventive events, shouldn't we rather marvel at the intensity with which MRI contrast agents were pursued despite the reigning pessimism regarding their usefulness in the equipment producer community?

Schering AG presented Gd-DTPA dimeglumine, a particular salt of Gd-DTPA, to a wider public for the first time in August 1983, during the second annual meeting of the Society of Magnetic Resonance in Medicine in San Francisco (43). At the same meeting, the group from the University of California at San Francisco, together with Weinmann, presented the first application of Gd-DTPA dimeglumine in myocardial imaging (28). After an uneventful preclinical development of Gd-DTPA dimeglumine at Schering AG, in November 1983 the product was first administered to man. In the formal phase I clinical trial at the Klinikum Charlottenburg of the Freie Universität, Berlin, under the direction of Roland Felix, all collaborators participated not only as experimenters, but also volunteered as subjects (44). During the development of a drug, almost nothing goes as planned, and this is what happened with Gd-DTPA. Insufficient coordination and control over clinical activities by the company led in December 1983 to unauthorized and premature studies of the product in patients. Fortunately for all persons involved and for the product, the studies went well and demonstrated contrast agent efficacy in some brain tumors (45). Overall, further clinical development went quite smoothly, considering the innovative nature of the product. The product gave ample opportunity to many academic radiologists, too many to be named here, to express their best. Frequently, the need to learn how to use the contrast agent and interpret the results was accompanied by parallel needs to deal with innovations on the machine side.

Beginning in early 1988, the pharmaceutical product Gd-DTPA dimeglumine 0.5 M for injection, now named Magnevist®, appeared in various markets, where it was very well received. Within a short time, contrast-enhanced MRI became a routine modality, e.g., for brain scanning.

Today, the product has a number of competitors on the market, such as gadoteridol/ProHance® (Bracco); gadobenate dimeglumine/MultiHance® (Bracco); gadoterate meglumine/Dotarem® (Guerbet); gadodiamide/Omniscan® (Amersham); gadobutrol/Gadovist® (Schering); and gadoversetamide/OptiMARK® (Mallinckrodt). Some of these agents even have advantages over gadopentetate dimeglumine/Magnevist® (Schering). Nonetheless, to date Gd-DTPA dimeglumine remains the market leader.

In the summer of 1982, Brasch, being an expert in contrast media in the X-ray field, developed an interest in such products for MRI. Nitroxide radicals had long been known as electron spin labels useful in biochemical research. Now, Brasch and collaborators demonstrated the novel utility as T1-shortening MRI contrast agents of this class of paramagnetic compounds in the form of water-soluble *N*-succinyl-4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl sodium salt (27,46–48). Elevated doses were needed to overwhelm the body's capacity to rapidly reduce the nitroxide to ineffective hydroxylamine derivative after intravenous injection. Subsequent to these pioneering experiments, similar nitroxide compounds were found to be sufficiently stable in cerebroventricular fluid to make possible MRI after intrathecal administration (49). Other efforts were aimed at patentable compounds or pharmaceutical formulations possessing improved water solubility, reduced tendency for bioreduction to hyroxylamine, and good tolerability (50). No product of this class has yet advanced to even the clinical candidate level.

Independently of all the efforts regarding soluble paramagnetic compounds, a second approach to MRI contrast agents was born, in the early 1980s. It had its point of departure in studies on cell separation technology. A few years earlier, separation of biological particles, including cells, based on tagging them with antibody-coated magnetic particles had been invented (51,52). Contemporaneously there had occurred the invention of certain improved magnetic particles consisting of dextran-coated colloidal magnetite (53), the mixed valence iron-(II,III) oxide Fe_3O_4. Biocompatible magnetic particles with improved properties and whose preparation was easier still were needed. Substantial efforts had been ongoing not only in several industries, but also at universities. Patenting activities mushroomed. At Thomas Jefferson University in Philadelphia, Charles S. Owen and Paul A. Liberti were working in the field. Magnetite particle technology per se was well known from the field of magnetic recording media production, as was the technology of stabilization of colloidal solutions for biological use by protection colloids. Colloidal dextran-stabilized iron-(III) oxide solutions were long-established injectable drugs. Owen and Liberti invented their own process for preparing magnetite nanoparticles in stable colloidal solution, a so-called biological ferrofluid. The nanoparticles consisted of small magnetite cores (diameter 50 to 70 nm) coated with bovine serum albumin.

In a completely different applicative context, Ohgushi et al. (54) had described utilization of the dextran-stabilized colloidal magnetite solutions of Hasegawa et al. (53) as a water proton T2 relaxation agent for NMR study of hydrogels. Their work made no mention of a possible use of the material in medical diagnosis. In addition, the

particle size of their preparation would have been excessive for intravenous use. Possibly triggered by the work of Ohgushi et al. (54), Owen had the insight that colloidal solutions of suitably sized magnetic particle would be a natural contrast media for MRI. The particles could be expected to be taken up by the reticuloendothelial system, where they should influence MRI signal intensity. He commissioned some exploratory MRI studies with his very small colloidal magnetic particles as new contrast agent in animals and worked in collaboration with radiologist Gerald L. Wolf at the University of Pennsylvania, in his hometown of Philadelphia. In the summer of 1982, finally possessing his own equipment, Wolf obtained the first images with the new class of contrast agent. As would be expected from the known pronounced enhancement of T2 relaxation in suspensions of magnetic particles and the known tendency of intravenously injected particles to localize in the reticuloendothelial system, the MRI contrast agent effect consisted primarily of signal reduction in the liver and spleen (55). That certain liver tumors contain no phagocytic cells gave immediately hope that the new contrast agent type could help in imaging liver tumors. Note that this all occurred before any information on the work with MRI contrast agents at Schering AG became public. It was through his collaboration with Mallinckrodt Inc. that Wolf was well aware of the industry's interests in MRI contrast agents.

In 1983, Liberti founded Immunicon Corporation, Huntington Valley, Pennsylvania, to commercially exploit the new class of magnetite particles both for cell separation and as MRI contrast agents. After moving to the University of Pennsylvania and on behalf of Immunicon Corp., Owen and collaborators concentrated on the former application alone. Both Thomas Jefferson University and Immunicon Corp. were interested in finding industrial partners for the development of products based on the new technology. Unable to generate industrial interest from several major pharmaceutical firms, in 1984 Owen and Liberti were given full intellectual property rights to their technology by the university. Under secrecy agreements with the presenting parties, in 1983 a number of companies involved in the contrast agent business were introduced to the concept of MRI contrast agents, particularly magnetite-based agents. The initial response was negative. The early perception of MRI contrast agents as superfluous and the subsequent change of mind are well exemplified by the case of Winthrop Laboratories, Division of Sterling Drug Inc., which in 1983 did not show any interest in the technology offered by Immunicon Corp. but in 1992 entered into a collaborative agreement.

The discoveries of MRI applications and the diligent efforts by Liberti and colleagues at Immunicon Corp. to learn how production processes were related to product characteristics allowed filing of U.S. patent applications (on October 4, 1985 and September 16, 1986) by Charles S. Owen, John C. Silvia, Louis d'Angelo, and Paul A. Liberti, with Immunicon Corp. as assignee.

The claims sought included both production processes for magnetic polymer particles and use of the products as MRI contrast agents. On October 3, 1986, the application was extended to Europe. Differences in patent law between Europe and the United States resulted in completely different outcomes in the two regions. In Europe, the contrast agent use of magnetic particles, but not their preparation method, became protected (56), whereas in the United States the inverse was the case (57). How this situation came about is discussed next.

Immunicon's efforts to gain patent protection for its inventions in the United States were repeatedly rejected because of the existence of prior art. Indeed there was a great boom in patenting of biocompatible magnetic particles. Apart from Owen and Liberti, others also had conceived and sought patent protection for the idea of using such materials as MRI contrast agents, without knowledge of the efforts of others at the time of patent application. Independent inventors of the MRI application were Ulf Schröder and Leif G. Salford (58) from the Neurosurgical Clinic of the Hospital in Lund, Sweden; Trond Jacobsen and Jo Klaveness (59) from Nycomed A/S; Truman Brown (60) from the Fox Chase Cancer Center in Philadelphia, PA; the group of Gries, Weinmann, Wolfgang Mützel, and Christian Zurth (61) from Schering AG; Ernest C. Groman and Lee Josephson (62) from Advanced Magnetics Inc.; and Kenneth J. Widder (63) from Molecular Biosystems Inc. Given the confused priority situation, Liberti persuaded the U.S. patent office that at least three patents regarding MRI with magnetic particles issued to competitor companies and cited as prior art were on identical art and that the matter should be settled on a first-to-invent basis. These arguments prompted the U.S. Patent Office to declare interference between Immunicon Corp., Advanced Magnetics Inc., Molecular Biosystems Inc., Nycomed A/S, and Schering AG. To avoid costly future litigation, a negotiated solution was agreed upon. Immunicon Corp., which in the meanwhile had made the strategic decision not to pursue MRI contrast agents, sold its intellectual property regarding MRI contrast agents to Nycomed A/S, and the latter retracted the MRI-related claims from its U.S. patent application. Nycomed A/S then reached agreements with the other companies regarding access to the contrast agent application technology. The path then was cleared for Advanced Magnetics Inc., as a start-up company and newcomer to the field of contrast agents, to blaze the trail toward commercial MRI contrast

agents based on magnetic particles. Unfortunately for the company, the trail turned out to be much more arduous and time consuming than expected. The pioneering product based on magnetic particle technology, AM125 or ferumoxides, first appeared on the market in 1995, distributed under license as Endorem® (Laboratoire Guerbet SA, France) or Ferridex® I.V. (Berlex Laboratories Inc., U.S.A.; Tanabe Seiyaku Co., Japan).

Once the feasibility of MRI contrast agents became public knowledge, the imagination of many investigators new to the field was ignited. The steeply increasing number of related publications in the following years testifies to interest (for reviews, see references 64 and 65). Some investigators focused on targeting products of the described classes to specific compartments or sites in the body. Others concentrated on finding novel ways to influencing MRI signal intensities. I reserve dealing with the ways these pursuits led to actual products for the future.

In summary, the conception of MRI contrast agent technologies in the forms that later affirmed themselves on the market occurred in the brief period from 1981 to 1982. It built on previously studied mechanisms for altering water proton relaxation rates and known classes of compounds, but it newly taught how this knowledge could be combined to achieve practical products with clinical utility.

The presented history illustrates the typical roles of academia and industry in technological innovation. The basic science foundation of technology is the domain of university-based research. Actual products that will succeed on the market typically are conceived within companies. Identification of the best place for technology in clinical practice is the result of academia–industry collaboration. It is completely outside the present scope to consider the many other factors that determine the success or failure of a product or even a whole technology. Certainly, conception of a new technology is a crucial phase, but it is just the first step on the march towards the technology's affirmation in clinical practice, the element that ultimately characterizes the technological innovation described by Schumpeter (1).

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