BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

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D E C I S I O N
of 11 February 1997

Case Number: T 0655/92 - 3.3.2

Application Number: 85900253.7

Publication Number: 0166755

IPC: A61K 49/00

Language of the proceedings: EN

Title of invention:
Diagnostic and contrast agent

Patentee:
NYCOMED AS

Opponent:
Advanced Magnetics Inc.

Headword:
Contrast agent for NMR imaging/NYCOMED

Relevant legal provisions:
EPC Art. 52(4), 54, 56, 84

Keyword:
"Clarity - (yes)"
"Diagnostic method within the meaning of Article 52(4) - (yes)"
"Novelty - (yes)"
"Inventive step - (yes)"

Decisions cited:
G 0005/83, T 0385/86

Headnote:
I. The use of a substance or composition for the manufacture of a preparation to be used in a specific method may derive its novelty from the subsequent use of the preparation in this specific method only if said method is one of those excluded from patentability by virtue of Article 52(2) EPC (see G 5/83, OJ EPO 1985, 64).

II. Methods for determining chemical or physical conditions which do not include any stages or measures requiring a doctor to carry them out but rather a technician in order to provide a basis for the doctor's subsequent activity of diagnosis may not necessarily fall within the exclusion of Article 52(4) EPC (see e.g. T 385/86, OJ EPO 1988, 308).

III. However, the diagnostic character of a process, within the meaning of Article 52(4) EPC, may be recognised in that such a process for which protection is sought does include essential steps which are to be implemented by medical staff or under the responsibility of a doctor (see reasons point 5.2).

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Headnote follows

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0655/92 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 11 February 1997

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 8 May 1992 revoking European patent No. 0 166 755 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
R. E. Teschemacher

Summary of Facts and Submissions

I. European Patent No. 0 166 755 was granted in response to European patent application No. 85900253.7, claiming the priority date of 21 December 1983.

II. Notice of opposition was filed by the respondents, requesting revocation of the patent in its entirety on the grounds of lack of novelty, lack of inventive step and insufficiency of disclosure (Articles 52, 54, 56, 83, 100(a) and (b) EPC).

The patent was revoked by the opposition division, mainly on the basis of the following documents:

(2) (J.S.G. Cox et al.); J. Pharm. Pharmacol, Vol. 24, 1972, 513-517, [(2) also in the decision under appeal];

(35) (M. Ohgushi et al.), J. Mag. Res., Vol. 29, 1978, 599-601 [(3) in the decision under appeal];

(13) (R. C. Brasch), Radiology, Vol. 147, June 1983, 781-788, "Work in Progress: Methods of Contrast Enhancement for NMR Imaging and Potential Applications" [(18) in the decision under appeal].

III. The decision was taken on the basis of the granted claims, as the main request, and two auxiliary requests.

Having recognised the novelty of the subject-matter of claim 1 of the main request, the opposition division considered that the claim did not involve an inventive step in the light of the teaching of Ohgushi et al. (35) when combined with the teaching of R. C. Brasch (13).

Ohgushi el al. describe dextran-magnetite particles falling within the scope of claim 1 and the results of *in vitro* experimental work intended to investigate their properties as a pore selective T2 relaxation reagent.

R. Brasch illustrates the common general knowledge of nuclear magnetic resonance (NMR) imaging technology with contrast agents shortly before the relevant date of the opposed patent.

The opposition division rejected the appellants' arguments that the invention lay in the use of **ferromagnetic** material for the manufacture of particles for use as a **negative** contrast agent in an *in vivo* method of NMR/imaging.

The division emphasised that the wording of claim 1 did not reflect the intended invention and contested the appellants' opinion that the expression "black holes" in the original description could be regarded as a valid disclosure, for the purpose of Article 123(2) EPC, for introducing into the text of the claim any term expressing the negative contrast effect.

The division also stressed that the results reported in the single example in the patent, evidenced the reduction of both T1 and T2 relaxation times as already anticipated by Brasch. Therefore no unexpected effect could be recognised in the claimed use of the contrast agent at issue.

Having regard to the auxiliary requests, the division maintained that the amendments added no further weight to the appellants' arguments, since they did not identify any negative contrast effect.

IV. The appellants (patentees) lodged an appeal against this decision.

Besides the documents already discussed during the proceedings before the opposition division, several further pre- and post-published documents were submitted. The documents have been designated as documents (1) to (72).

The following are relevant to the present decision:

(2) (Cox et al.) supra;

(12) (R. C. Brasch et al.), Society of Magnetic Resonance in Medicine, First Annual Meeting, 16-18 August 1982, "Evaluation of Nitroxide Stable Free Radicals for Contrast Enhancement in NMR Imaging", pp. 25-26;

(13) (R. C. Brasch) supra;

(14) (R. C. Brasch et al.), Radiology, June 1983, 773-779, "Work in Progress: Nuclear Magnetic Resonance Study of Paramagnetic Nitroxide Contrast Agent for Enhancement of Renal Structures in Experimental Animals";

(28) (H. J. Weinmann et al.), Society of Magnetic Resonance in Medicine, Second Annual Meeting, 16-19 August 1983, "Paramagnetic Contrast Media in NMR Tomography - basic properties and experimental studies in animals", pp. 370-371;

(35) (Ohguhshi et al.) supra;

(39) (Z. Abe, K. Tanaka et al.), US-A-3 932 805;

(45) (M.R. Goldman et al.), Circulation, Vol. 66, No. 5, November 1982, "Quantification of experimental myocardial infarction using NMR-imaging and paramagnetic ion contrast enhancement in excised canine hearts" pp. 1012-1016;

(46) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics", 6th edition, pp. 1322-1326 (1980);

(63) (K. Tanaka, Z. Abe et al.), Sogo Rinsho, Vol. 30, No. 10, 1981, pp. 2609-2615 & English translation, "Observation of Physiological Functions by Nuclear Magnetic Resonance (II)" pp. 1-27;

(67) G. L. Wolf et al., Magnetic Resonance Annual, 1985, "Contrast agents for Magnetic Resonance Imaging", pp. 231-266.

V. The appellants' position can be summarised as follows.

By the priority date of the opposed patent, NMR imaging technology was still in its infancy. The most attractive feature was its non-invasive nature, whilst its inherent drawback was low signal intensity.

In an effort to develop and improve the technology, many possible directions were being investigated by late 1983.

Among other measures, the use of contrast agents was contemplated, though many authors expressed concern that this artefact would transform the NMR imaging into an invasive technique.

Starting from this background, the appellants explained that the intended invention of the opposed patent was the use of ferromagnetic material for the manufacture of a diagnostic agent for use as a **negative** contrast agent in an *in vivo* method of NMR imaging.

Unlike the contrast agents in the prior art, the contrast agent of the invention caused a reduction, rather than an enhancement, in the intensity of the NMR signal.

Referring to (13), they stressed that, since the first reports on contrast agents in NMR technology, only paramagnetic contrast agents had been described, which predominantly increased the intensity of the signal.

The appellants further pointed out the many reservations within the scientific community, about the use of ferromagnetic materials in NMR imaging *in vivo*.

Because of this general opinion, the first reports on the use of ferromagnetic contrast agents did not appear until long after the relevant date of the patent at issue.

VI. The respondents (opponents) did not reply to the statement setting out the grounds of appeal and declared that they were withdrawing from the appeal proceedings.

VII. As a reaction to the communications issued by the board, in which *inter alia* the latter expressed doubts concerning the medical nature of the NMR imaging method set out in the invention, an amended form of claim 1 according to the main request was filed on 22 April 1996. The claim reads:

"Use of a magnetically responsive material for the manufacture of a diagnostic contrast agent for use in a method of in vivo nuclear magnetic resonance imaging of a subject, said agent comprising particles of a matrix material having a diameter of up to 10 micrometres and having enclosed therein a said magnetically responsive material the magnetic responsiveness of which is such that said particles are magnetically localisable and such that said particles in said nuclear resonance imaging of said subject cause relaxation time changes resulting in a visualisable 'black hole' contrast effect".

VIII. The appellants requested maintenance of the patent in the amended form of 22 April 1996, as their main request, or in the form of one of the two auxiliary requests enclosed in the statement setting out the grounds of appeal.

Reasons for the Decision

1. The appeal is admissible.

2.1 Article 123(2) EPC

The subject-matter of the amended claim 1 according to the main request is described in the original application, specifically on page 5, line 35 to page 6, line 6, on page 2, line 32 to page 3, line 1 and on page 5, lines 5 to 9. The feature that "said particles ... cause relaxation time changes resulting in a visualisable *black hole* contrast effect" is described *expressis verbis* on page 2, lines 12 to 20.

The requirements of Article 123(2) EPC are therefore satisfied.

2.2 Article 123(3) EPC

The set of claims according to the main request differs from the granted claims as regards claim 1 only. The text of the amended claim 1 comprises the additional features: "*contrast*" referring to the diagnostic agent and "*in vivo*" referring to the nuclear magnetic resonance imaging. Both features define more precisely the manufactured agent and the method in which the agent is used. Therefore they do not extend the protection conferred by the granted patent.

Moreover the particles of amended claim 1 are characterised by: "*having enclosed therein said magnetically responsive material, the magnetic responsiveness of which is such that said particles are magnetically localisable and such that said particles in said nuclear resonance imaging of said subject cause relaxation time changes resulting in a visualisable 'black hole' contrast effect*". This characterisation of the particles is more precise than the characterisation in the granted claim 1 which covered the unlimited use of **any magnetically responsive material.** Therefore it represents a limitation of the protection conferred by the granted claims. Hence the requirements of Article 123(3) EPC are fulfilled.

3. Article 84 EPC

Since claim 1 according to the main request is in amended form, compliance with the requirements *inter alia* of Article 84 has to be considered. Indeed the expression "black hole contrast effect" was objected to by the respondents during the proceedings before the opposition division and the issue was considered in the decision under appeal.

The expression "black hole" is traditionally taken from the language of astronomy and identifies a hypothetical region of space resulting from the gravitational collapse of a star. The gravitational field around the region would be so high that neither matter nor radiation could escape from it (cf. Collins, Dictionary of the English Language, second edition 1986).

Thus the region of space designated as a 'black hole' is visualised not because of an emitted signal, but rather because of the lack of any signal versus a surrounding background which emits radiation.

The general knowledge on NMR imaging by the relevant date of the opposed patent is illustrated by (13), (14) and (45), though many other equivalent pieces of prior art were quoted during the proceedings.

According to this background, the skilled person knew that the different anatomical parts submitted to NMR imaging were represented as bright or dark areas, which corresponded to areas of high or low emission, ie of high or low signal intensity. This relationship between intensity and brightness or darkness of the NMR image is recognised eg in (14) that reads (cf. commentary on figure 1) "... normal urine in the pelvocalyceal structures **is** [of] **very low intensity and thus appears black** (emphasis added), or in (45) which reads (cf. page 1015, left-hand column, last paragraph): "Manganese probably differentially shortens T1 relative to T2, which results in **increased signal intensity and image brightness. The infarct, ... , appears dark** " (emphasis added). Equally explicit is figure 4 of (13) which illustrates the increased brightness accompanying the increase in NMR signal intensity due to Cu++, Fe++ or SFR versus water, urine, fat or Mn++ in low concentration.

The person skilled in NMR technology was also aware, eg from (13), that the intensity of the NMR signal is influenced by the parameters T1 and T2 relaxation times, and that the contrast agents emphasise the difference in brightness between adjacent zones by modifying the value of T1 and/or T2 in the different tissues. The relationship between these parameters and the NMR signal intensity is illustrated by the equation given on page 782 in (13). According to this equation, a short T1 relaxation time corresponds to a high image intensity, while a short T2 relaxation time corresponds to low image intensity (cf. page 782, right-hand column, second paragraph).

Therefore, assisted by said general knowledge, the skilled reader would immediately understand from the expression "black hole", when referring to "contrast effect" and transferred to the NMR imaging technology, that the effect of the claimed contrast agent is that of modifying the relaxation times in such a way to depress the signal released in those tissues perfused by said agent, which finally results in dark or black spots (ie a black hole) on the image.

This interpretation would find confirmation in the single example in the patent. The data reported therein show that the contrast agents at issue exhibit a T2 decreasing effect which is unambiguously predominant over the T1 effect. Indeed, for any concentration of contrast agent, the per cent decrease in T2 relaxation time is dramatically higher than that of the T1 relaxation time. A drop in NMR signal and brightness would therefore be expected.

In conclusion, the Board holds that the expression "black hole contrast effect", seen in the context of the NMR imaging technology, is clear to the skilled reader, notwithstanding the original meaning of "black hole" that, in a strictly literal interpretation, and as pointed out by the respondents, would indicate a total lack of signal rather than a decreased signal.

4. Article 83 EPC

As admitted by the parties and as discussed later on in this decision, the particles of the invention, consisting of a matrix material having enclosed therein a magnetically responsive material, were commercially available, for therapeutical purposes, long before the priority date of the patent. Thus the definition of the diagnostic agent in itself is no reason for an objection pursuant to Article 83 EPC. Besides, the production of dextran-magnetite particles is disclosed in the example in which the property lying at the basis of the invention, namely the predominant T2 effect, is proved experimentally.

As to the *in vivo* NMR imaging method in which the contrast agent is used, the Board's opinion is that by the priority date of the patent a great deal of literature concerning the general principles and many practical applications of NMR imaging technology with or without contrast agents had already been published. By way of example, the aforementioned documents (13) or (14) may be quoted as illustrative of the level of knowledge in this specific field.

Therefore, in the Board's judgment the invention is described in a manner sufficiently clear and complete to meet the requirement of Article 83 EPC.

5. Article 52(4) EPC

5.1 As acknowledged in the patent description, the agent of claim 1, which comprises particles of a matrix material having a diameter of up to 10 microns and having enclosed therein a magnetically responsive material, have been known in the prior art as a haematopoietic medicament for intravenous or intramuscular injection in the treatment of iron deficiency since about 1965.

More specifically, document (35) discloses the use of dextran-magnetite (triiron tetroxide) particles, having a diameter of 5 to 20nm. The compound is said to be *related to the iron-dextran complex (1) utilised as a haematopoietic and made by adding dextran to a suspension of triiron tetroxide* (cf. first paragraph). Reference (*1*) (Ricketts, Cox et al. Nature 208, 237, 1965) apparently represents one of the first reports on this complex.

Also (2) describes an iron-dextran complex designated as "Imferon" (see footnote on page 513). As is evident from the quotation from the aforementioned Ricketts, Cox et al. (cf. page 513, line 12), "Imferon" is the same complex as that disclosed in (35).

Finally, document (46) refers again to "Imferon" ie *Iron Dextran Injection* U.S.P. as *the parenteral preparation in general use in the United States at the present time.* (cf. page 1325).

The Board can therefore conclude that all three prior documents relate to the same particles according to claim 1 and their first therapeutic application.

5.2 For this reason, during the proceedings before the examining division, claim 1 was drafted in the form for the protection of the "second medical indication" of a medicament, according to the decisions G 1/83 (OJ EPO, 1985, 60), G 5/83 (OJ EPO, 1985, 64) and G 6/83 (OJ EPO, 1985, 67).

Whether or not the use of a substance for the manufacture of a "preparation" may derive its novelty from the subsequent use of said "preparation" in a specific method, depends on the nature of the method itself. The answer is in the affirmative only if said method is one of those excluded from patentability by virtue of Article 52(4), (cf. G 5/83 (supra), point 21, last paragraph). Therefore, in order to assess the novelty of the subject-matter of claim 1, it first has to be established whether the present claim 1 refers to one of those methods or, alternatively, to a technical method susceptible of patent protection.

The policy behind the exclusion of the methods defined in Article 52(4) EPC was to ensure that those who carry out such methods as part of the medical treatment of humans or the veterinary treatment of animals should not be hampered by patents (T 385/86, OJ EPO 1988, 308, point 3.2). The intention was only to prevent non-industrial medical and veterinary activities from being restrained by patent rights (G 5/83, supra, point 22). When Article 52(4) EPC is being interpreted, this purpose has to be taken in consideration.

With regard to methods for obtaining chemical/physical data from inside the living body by means of diagnostic apparatus registering these data or reproducing images, the Boards have ruled that these do not fall within the exclusion of Article 52(4) EPC and that only such methods are excluded which provide results immediately enabling a decision to be taken on a particular line of

medical treatment (T 385/86, supra, and the other decisions cited in Case Law of the Boards of Appeal, 2nd edition, 1996, I.A. 2.5). This ruling was based on the consideration that in such methods the step sequence for which protection is sought does not include any stage having the character of medical diagnostic activity or medical treatment or any measure requiring a doctor to carry them out. Rather the method therein claimed could be carried out by a technician in order to provide a basis for the doctor's subsequent activity of diagnosis (T 385/86, supra, points 3.5.1 and 3.5.2).

5.3 The nature of the process according to claim 1 of the patent at issue is quite different. The method is an *in vivo* NMR imaging technique using contrast agents. Unlike the technique envisaged in T 385/86, supra, the method of the present invention is characterised by the parenteral administration (iv) of the contrast agent of claim 1, which transforms the NMR imaging from a non-invasive to an invasive technique. Additionally the intravenous injection of dextran-magnetite, ie Imferon (see point 5.1 of the decision), is not devoid of any risk of side-effects, some severe, as is well documented by (46) which reports at page 1326, right-hand column, that:

> *Reactions to intravenous iron include headache, malaise, fever, generalised lymphadenopathy, arthralgias, urticaria and in some patients with rheumatoid arthritis, an exacerbation of the disease. Of greatest concern, however, is the rare anaphylactic reaction, which may be fatal in spite of treatment. While only a few such deaths have been reported, it remains a deterrent to the use of iron dextran.*

In consideration of the risk inherent in the treatment, it is further suggested that:

> *The technique of intravenous administration involves first the injection of 1 or 2 drops of iron dextran over a period of 5 minutes to determine whether any signs or symptoms of anaphylaxis appear. If not, 500 mg of iron may then be injected over a period of 5 to 10 minutes.*

It is indisputable that the task of "*determining whether any signs or symptoms of anaphylaxis appear*" can only be the responsibility of medical staff who have to recognise the earliest symptoms of anaphylaxis or any other undesired reaction and accordingly either have to adapt the treatment to the specific situation, or interrupt the administration or even undertake without delay all those measures necessary to control and minimise the side-effects already evident.

Therefore, unlike the processes of the previous cases, the present diagnostic process, when considered in its totality, comprises at least one step essential for the desired diagnostic result, which cannot fall under the exclusive responsibility of the technician skilled in NMR technology. While for a process whose steps as a whole are non-medical but technical it is legitimate not to derive the *in vivo* diagnostic character from its final diagnostic purpose, this does not apply to a process for a diagnostic purpose which is to be implemented in its essential steps by medical staff or under the responsibility of a doctor. A different interpretation would be in clear conflict with the spirit of Article 52(4) EPC.

Finally it is recognised that, in the present case, the skilled person, namely the competent medical staff, is not necessarily represented by one single specialist.

In fact, it may well be the case that the doctor competent for the final diagnostic activity is not the specialist competent for carrying out and controlling the medical part of the diagnostic method, that is, injecting the contrast agent and undertaking all the subsequent therapeutical measures, should they prove necessary. This situation does not modify the medical nature of the diagnostic process of claim 1. On the contrary, it shows that, being the activity of the specialist administering the contrast agent independent from the activity of the specialist making the final diagnosis, the diagnostic character, within the meaning of Article 52(4) EPC, can also be recognised in consideration of the medical character of some steps of the said method and independently from the final diagnostic activity which, indeed, is not part of the claimed process.

In conclusion, the process according to claim 1 is, in the Board's judgment, a diagnostic method within the meaning of Article 52(4) EPC.

6. Article 54 EPC

Besides the prior art documents (2) and (46), which are not prejudicial to the novelty of the present invention since they disclose particles of dextran-magnetite for use in the treatment of iron deficiency anaemia, the same complex is described in (35) as a new pore-selective T2 relaxation reagent.

Ohgushi et al. (35) investigate the properties of 5 to 20 nm large particles as a proton relaxation enhancer in an *in vitro* aqueous system (Sephadex G75 gel) simulating the biological situation of cells and intracellular spaces. The results reported in figures 1

and 2 suggest that dextran-magnetite is an excellent pore-selective reagent since it is excluded from the interior of the gel particles, while the reference agent, manganese chloride, is free to permeate the same particles.

Unlike the opposed patent, which relates to the *in vivo* use of the complex of claim 1, (35) describes the use of dextran-magnetite in an *in vitro* analytical method. A second and more important difference is that (35) does not refer to the NMR imaging technique, but simply discloses the spectroscopic (spin-echo) measurement of **one** of the parameters underlying the NMR imaging technique, ie the transverse relaxation time (T2), and the determination of the influence of the relaxation reagent on said parameter. Basically, (35) does not disclose the use of dextran-magnetite as a contrast agent in NMR imaging, but the use of this complex as a T2 relaxation time reagent.

Therefore document (35) does not affect the novelty of the subject-matter of claim 1.

Document (13) was also considered during the proceedings. This piece of literature is a report on methods of contrast enhancement in NMR imaging known by 1983 and their potential applications. The document illustrates the general principle of NMR contrast enhancement and analyses in more details the properties of the different classes of potential contrast agents. However (13) does not contemplate contrast agents comprising particles of a matrix material having a diameter of up to 10 micrometers and having enclosed therein a magnetically responsive material, whose responsiveness is typical of the ferromagnetic substances.

Since no other more pertinent piece of prior art was provided, the Board holds that the subject-matter of claim 1 is novel.

7. Article 56 EPC

7.1 Document (35) was cited in the decision under appeal as the closest prior art, combined with (13). During the opposition procedure, (35) was also considered by the respondents in combination with (39) (Z. Abe). The Board does not share the opinion that (35) represents the closest prior art, since, as has already been seen, this document does not relate to NMR imaging, but to the evaluation of the potential **pore-selectivity** of dextran-magnetite as a relaxation enhancer in a different technique, that is the measurement of T2 relaxation time in itself.

In the Board's view, (13) represents the closest prior art. This document, like the opposed patent, concerns, in fact, contrast enhancement in the *in vivo* NMR imaging technique. Therefore the Board recognises a relationship of direct continuity between the present invention and the teaching in (13), which cannot be envisaged when (35) is taken as the closest prior art.

7.2 The technical problem underlying the present invention is the provision of further forms of NMR imaging which would eventually enlarge the potential applicability *in vivo* of this technique.

7.3 The solution of the technical problem proposed by the opposed patent is the use of contrast enhancer agents according to claim 1 which, on the other hand, are already known as T2 relaxation reagents from (35) or as haematopoietic agents from (2) and (46).

7.4 According to the appellants, the contrast enhancement is achieved by decreasing, instead of increasing, the intensity of the signal emitted from those areas perfused by the claimed contrast agent. For this reason, such areas finally result, in the NMR image, as dark or black areas. This type of contrast mechanism, which has been defined as **negative** contrast, identifies a new concept of contrast enhancement and qualifies a new form of NMR imaging technique with a contrast agent.

Although the patent disclosure does not contain any full illustration of *in vivo* NMR imaging, the passage in the original description "*black holes are formed around each particle which may be visualized and thus give an impression of the vessel density in the tissue in question*" is regarded as an indication that the desired effect has been successfully obtained by applying the novel technique. This indication is confirmed by the single example, which indisputably provides evidence that the claimed contrast agents have the property underlying the invention, that is, the predominant decreasing activity of the T2 relaxation time over the T1 relaxation time.

The validity of the proposed solution, and the reliability of the statement of success in the patent, is further confirmed by late published pieces of literature, such as (67), pages 263, 264, which relates to the properties of ferromagnetic particles as a negative contrast agent and which disclose the application of the novel concept of NMR imaging as first described in the opposed patent.

In conclusion, the Board is satisfied that the underlying technical problem is solved by the invention.

7.5 Beyond any doubt, the proposed solution is not suggested by the closest prior art, document (13), which does not envisage contrast agents comparable to the agents of the invention.

7.6 On the other hand, whether the proposed solution was obviously derivable from the teaching in (35) can only be assessed by keeping in mind the general knowledge on NMR technology, NMR imaging and NMR contrast agents at the priority date of the patent under appeal.

7.6.1 Nuclear magnetic resonance is a general expression which qualifies the basic concept underlying different techniques and different applications.

K. Tanaka, Z. Abe et al. [(63-English translation)] schematically illustrate and classify in Fig. 17 the medical applications of the NMR measuring method known by 1981. "**NMR imaging**" would appear to be the most complex application and is based on the computer-assisted mathematical analysis of the different NMR signals (T1, T2 , Intensity) taken alone or together. The "**Local NMR measuring method**" represents another application. The measurement of the basic signals T1 or T2 relaxation times of parts of the target body is, in itself, a technique which can already give a spectrum of internal chemical and physical information without the need of being re-elaborated into an image but simply by way of a linear representation of punctual values in a graph. A technique belonging to this group would appear to be the Magnetic Field Focusing Method disclosed in (63), from page 14 to the first paragraph of page 18, or in (39).

Unlike in NMR imaging, in the local T1 or T2 measurements, where the T1 or T2 value in itself gives information, the significance of the analysis depends only on the entity of the variation in T1 or T2 among different areas of the target body, regardless of the mathematical sign of this variation. Thus either a decrease or an increase in either T1 or T2 may be equally significant for the final information.

The technical teaching in (35) resides in this latter situation. In fact the objective of the analytical method in (35) is the measurement, by way of spin-echo, of the transverse relaxation time (T2) and the results obtained are expressed in terms of the absolute values of T2 in a graph as shown in Figures 1 and 3.

7.6.2 On the basis of this background, the question is whether it would have been obvious for the person skilled in the art to use the dextran-magnetite complex of (35), proved to be a T2 relaxation reagent, for the manufacturing of a contrast agent in the NMR imaging technique.

7.6.3 The Board is aware that, in general terms, a contrast enhancement may be achieved either by increasing or decreasing the intensity of the signal released by the parts perfused by the agent. In both cases, the contrast between those parts and the surrounding areas would be enhanced.

However, in the specific domain of NMR imaging and by the priority date of the patent, and even later, the skilled person had a different and more limited concept of contrast agents. As proved by the prior documents discussed below, he normally identified the contrast enhancement with a **signal intensity enhancement** and, accordingly, with brighter areas.

Figure 4 of (13) illustrates the effect of a number of potential contrast enhancers. The explanatory text states that:

> *"The solution of stable free radicals, ferrous ions (Fe^{+2}) and cupric ions (Cu^{+2}), all in 10 mmol/L concentration, produce a dramatic increase in NMR intensity, when compared with water or urine. These potential NMR contrast enhancers, as well as manganous ions (Mn^{+2}) are paramagnetic substances ..."*

Document (12), (1982) evaluates nitroxide stable free radicals (NSFR) for their ability in contrast enhancement. The authors report (cf. page 25, line 19 to 24) that:

> *"within tissues these effects [of NSFR] result in an increase in intensity on the NMR image using relatively low concentrations of NSFR. A 0.5 mM concentration of NSFR in water has a notably stronger intensity signal than water or urine; the intensity image of 10.0mM NSFR solution is very bright":*

Document (45) too, describes the properties of manganese as a contrast agent. The authors stress (cf. page 1015, bottom of the left-hand column) that:

> *"Manganese dramatically shortens T1 in myocardial tissues ... which results in increased signal intensity and image brightness. The infarct, which does not receive manganese, remains at its "normal" signal intensity and appears dark ..."*

Finally (28) illustrates, even more explicitly, the concept of contrast agents (CM) in August 1983. The article reports (cf. page 370, "Results") the operating conditions to be used in order to achieve the highest contrast enhancement with GdDTPA, a well known contrast agent chelate. The text reads:

> *"In NMR tomography the contrast agents (CM) increase the signal intensity to a certain extent depending on the concentration and magnetic properties of the substances tested. However, after reaching an optimal effect, any higher concentration of CM decreases the signal. Highest intensities were achieved with concentrations of CM in the millimolar range.*
>
> *Best results are obtained by using pulse sequences that emphasize the T1 effect".*

All the cited documents are illustrative of the accepted meaning attributed to "contrast enhancer agent" in the scientific community concerned with NMR imaging technonogy at the relevant date of the opposed patent. This meaning usually covered relaxation reagents, mainly paramagnetic ions, characterised by a T1 relaxation activity predominant on the T2 relaxation activity with the final effect of increasing the intensity of the emitted signal. The areas subjected to contrast were therefore expected to be highlighted as brighter spots over the dark surrounding background.

7.6.4 The attention of the skilled reader of (35) would have been immediately drawn to the strong T2 decreasing activity of the dextran-magnetite complex. Assisted by the general knowledge provided by (13), that any decrease in T2 brings about a corresponding decline in the NMR signal intensity, the skilled person would have very easily predicted the loss in signal efficacy due

to dextran-magnetite. Therefore, he would have found no motivation to contemplate the use of this relaxation reagent as a contrast agent for *in vivo* NMR imaging, since this was in clear contradiction to the concept of "NMR contrast agent" as accepted at that time and as discussed above.

Nor is the Board able to recognise any reference to the *in vivo* NMR imaging technique in the sentence in (35):

> "*In the NMR measurement of water in biological systems such as blood, muscle and other tissues it is useful to control the relaxation rate of extracellular water without disturbing the relaxation rate of water in closed cells.*" (cf. page 599, 2nd paragraph).

In fact, it is noted from all the prior art documents quoted during the appeal proceedings that the first reports on the use of contrast agents in NMR imaging appeared in the early 80's, whilst (35) dates from 1978. Therefore the person skilled in the art had no reason to interprete the document in the light of a general common knowledge which became available only years later. As a matter of fact, the experimental work described in (35) was intended to investigate the properties of dextran-magnetite as a potential pore-selective reagent which could, if proved successful, open up new possibilities for the selective control of the relaxation rate of the extracellular water, without disturbing the relaxation rate of water in closed cells. However, in the light of the technical teaching in (35), the potential as a contrast agent in *in vivo* NMR imaging remained to be proved

On the basis of the above consideration, the Board is of the opinion that the subject-matter of claim 1 is not derivable in an obvious way from the combined teaching of (13) and (35).

7.6.5 Even less relevant, in the Board's judgment, is the teaching in (39) (Z. ABE).

Document (39), like (35), does not describe an NMR imaging technique, but relates to the different aspects and applications of a method that is, or is very close to, the Magnetic Focusing Method disclosed by the same authors in (63) (supra). The method is based on the differentiation of the resonance frequency of a liquid, such as water, in different and adjacent tissues having nuclear magnetic moment placed in a static magnetic field. *In vivo* selective measurement of the relaxation time of a particular part of the target body is possible by way of said method.

The use of ferromagnetic powder (ferrite) is suggested according to the second embodiment of the invention of (39) (cf. column 8, line 44 to 62). However, beside the fact that the ferromagnetic material is not used in the form of a complex according to claim 1 of the patent under appeal, ferrite is not said to act as a contrast agent in the NMR imaging technique, in the sense of a relaxation time enhancer, but as an agent which, due to its own stable magnetic field, is capable of locally influencing the field intensity of the static magnetic field and thus facilitating the discrimination of the resonance frequency of those areas comprising said agent over the neighbouring regions. As for (35), the person skilled in the art could not find in (39) any motivation or suggestion to extend the use of ferrite or any other ferromagnetic substance to different techniques and to a different purpose.

7.6.6 With reference to (2) and (46), which relate to the therapeutical indication of dextran-magnetite as a haematopoietic medicament, the Board does not recognise any relevance in these prior documents since no apparent relationship in mechanism can be envisaged between the iron reintegrating activity developed by dextran-magnetite in the treatment of iron deficiency and the activity as a NMR contrast agent based on the inherent ferromagnetic properties of some iron salts.

On the basis of the above discussed reasons, the Board holds that the subject-matter of claim 1 according to the main request involves an inventive step within the meaning of Article 56 EPC.

Since the patent can be maintained on the basis of the appellants' main request, it is not necessary to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent as amended with the following claims and a description to be adapted:

   Claims 1 to 10 of the main request filed with the letter of 22 April 1996.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon