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# D E C I S I O N
# of 1 July 1997

**Case Number:** T 0469/94 - 3.3.2

**Application Number:** 86113026.8

**Publication Number:** 0217258

**IPC:** A61K 31/14

**Language of the proceedings:** EN

**Title of invention:**
The use of choline or choline releasing compounds in the production of pharmacological compositions capable of reducing fatigue

**Applicant/Patentee:**
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

**Opponent:**
-

**Headword:**
Perception of fatigue/MIT

**Relevant legal provisions:**
EPC Art. 123(2), 52(4), 54

**Keyword:**
"Non-therapeutic treatment of the human body (yes)"
"Novelty (yes): new and distinguishable non-therapeutic application of choline"
"Invention step (yes): not suggested effect"

**Decisions cited:**
T 0081/84, T 0290/86, T 0780/89, T 0655/94, G 0002/88

**Catchword:**
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Case Number: T 0469/94 - 3.3.2

# D E C I S I O N
## of the Technical Board of Appeal 3.3.2
## of 1 July 1997

**Appellant:** MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 Massachusetts Avenue
USA - Cambridge, MA 02139 (USA)

**Representative:** Tauchner, Paul, Dr.
Vossius & Partner
Postfach 86 07 67
DE - 81634 München (D)

**Decision under appeal:** Decision of the Examining Division of the European Patent Office posted 9 December 1993 refusing European patent application No. 86 113 026.8 pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** P. A. M. Lançon
**Members:** C. Germinario
J. H. Van Moer

**Summary of facts and submissions**

I. European patent application No. 86 113 026.8 (publication number 0 217 258) was refused by the examining division under Article 97(1) EPC on the grounds of lack of inventive step of the subject matter of claim 1. The decision was taken on the basis of a set of claims directed to the protection of the second medical indication of choline or a choline derivative, the medical indication being the reduction of muscular fatigue in a patient having completed major exercise.

II. It was the examining division's view that the use of choline in reducing fatigue in a patient was known from the documents:

(1) Neurology, Vol. 30, No. 12, 1980, 1334-1336 and
(2) EP-A-18 550.

The examining division considered that the treatment with choline of muscle diseases and hardness disclosed in (2) was equivalent to or even a synonym for the treatment for reducing muscle fatigue according to the application. It held that the present applicant had simply found another explanation for the mechanism of action for choline which was not considered as evidence of an inventive step.

Moreover, in view of EP-A-1 924 (ie document 3), which described pharmaceutical compositions comprising a choline-derivative dissociating, after administration, into free choline, the examining division concluded that it was a matter of routine for a person skilled in the art to make a preparation as claimed for the treatment of muscle fatigue.

III. The appellants lodged an appeal against this decision, filing two amended sets of claims 1 to 3 as main and auxiliary petitions and requesting oral proceedings as an auxiliary measure.

They argued that the invention was based on the discovery that the blood choline level falls markedly after major exercise and that the administration of choline or a derivative thereof proved effective, in different trials, in maintaining the vigour and decreasing the perception of fatigue in persons performing or having completed major exercise (runners, basketball players and swimmers). Therefore the object of the present invention was that of treating or preventing the perception of fatigue as a feeling of weariness. For this reason the expression "pharmacological composition" in claim 1 was not intended in the sense of therapeutical composition to heal a disease as was the case in (2). This document disclosed the treatment of muscle diseases which were neither comparable with nor a consequence of fatigue but always the manifestation of a pathological state independent of fatigue and having an origin and development different to those of fatigue.

With reference to document (1), the appellants contended that no conclusion could be drawn that the reported less post-seizure fatigue observed in epilepsy patients treated with choline was caused by the administration of choline rather than by the shorter duration of the complex partial seizure.

IV. The board issued a preliminary communication in which it questioned the pertinence of the formulation of the claims in the form of second use in the therapeutic domain.

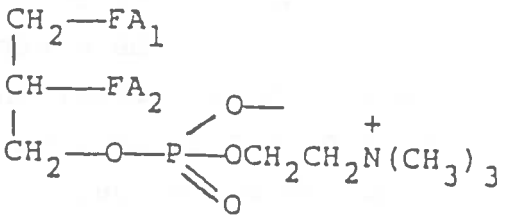
Moreover, in consideration of the fact that the prophylactic administration of choline would necessarily also prevent, beyond the perception of fatigue, the muscular diseases cited in (2), an objection of lack of novelty over said prior document was envisaged.

V. As a reaction to the communication from the board, a new set of claims 1 to 3 was filed on 27 June 1997, as main request, having the form of the protection of the second **non-therapeutic** use of a product. Two further sets of claims 1 to 3 were also filed as first and second auxiliary requests.

VI. Oral proceedings were held on 1 July 1997. The appellant's representative was accompanied by an expert (Mr. L. D. Lepene).

VII. Claim 1 of the main request reads:

"The use of a compound of the group of choline or a salt of choline, lysolecythin, glycerophosphocholine or an acylglycerophosphocholine having the formula



wherein FA1 and FA2 can be the same or different and are fatty acid residues having from 6 - 26 carbon atoms, in an amount effective to raise the bloodstream choline level of a person to between 10 and 50 nmoles/ml, for increasing the acetylcholine level in the brain and the tissue and thereby reducing the perception of fatigue in a person about to participate in major exercise or in a person having completed major exercise".

VIII. The appellants request that the decision of the examining division be set aside and that the patent be granted on the basis of one of the amended sets of claims 1 to 3, according to the main request, first auxiliary request or second auxiliary request submitted by telefax dated 27 June 1997.

**Reasons for the decision**

1. The appeal is admissible.

*Main request*

2. *Article 84 EPC*

It is the board's view that the subject matter of amended claims 1 to 3 is clear, concise and supported by the description.

3. *Article 123(2) EPC.*

The amended claim 1 includes the subject matter of claims 1 and 2 as originally filed. The additional part of the claim represented by the expression: "for increasing the acetylcholine level in the brain and the tissue" is disclosed in the first paragraph of page 1 and in the third paragraph of page 2 of the original application. A further amendment is the expression "reducing the perception of fatigue" which replaces the expression in the original application "reducing the fatigue". In the board's view, the amendment does not represent an extension of the content of the original application, since there seems to be a direct and inextricable correlation between the biochemical state qualified as "fatigue" and the consciousness of this state. Therefore, the concept of fatigue identifies the concept of "perception of fatigue" to the effect that a

reduction in the perception of fatigue reflects the reduction of fatigue. A further amendment is the replacement of "patient" by "person". From the context of the original application it is clear that the subjects submitted to the treatment with choline are healthy persons capable of voluntarily performing a major exercise. Therefore the word "patient" is improperly employed in the original document as a synonym for "person". The last amendment is the reversal of claim 1 to the form of a use-claim in the non-therapeutic domain. The use of choline or a choline derivative for increasing the acetylcholine level and thereby reducing fatigue is unambiguously disclosed in the original application. Therefore, in the presents circumstances, the amendment has a merely formal effect without any implication as to Article 123(2) EPC. The same conclusion applies to claim 2 where "pharmaceutical composition" has been replaced by "compound", in order to acknowledge the non-therapeutic use of choline or a derivative thereof.

Summing up, the main request fulfils the requirements of Article 123(2) EPC.

4. *Patentability of the use-claim.*

4.1 The subject matter of claim 1 is the use of choline or of a choline derivative in a method for treating the human body. The patentability of this subject matter depends on the nature of such treatment. Should it be therapeutical or surgical, the use-claim would be excluded from patentability pursuant to Article 52(4) EPC.

Therefore the question is whether increasing the acetylcholine level in the brain and tissue and thereby reducing the perception of fatigue in a person about to

participate in major exercise or having completed major exercise counts as therapeutic or non therapeutic treatment of the human body.

4.2 The condition of fatigue induced by the performance of exercises is a transitory physiological condition caused by natural circumstances and removable by simple rest. Simple training is generally known as retarding the perception of fatigue. Pain or serious suffering do not appear to be manifestations of fatigue, which therefore is not comparable with the pathological state typical of a disease or an injury. The treatment for reducing the perception of fatigue is not even comparable with the relief of pain, discomfort and incapacity considered in decision T 81/84 (OJ EPO, 1988, 207). In that case, the competent board was called upon to decide whether the treatment of menstrual discomfort should fall under the category of therapeutic treatment. The board took the decision that whenever a person is suffering from the manifestations of a given condition, though natural, and whenever these manifestations overlap with or are indistinguishable from the symptoms of a disease or an injury, the treatment with any substance providing healing or relief should be considered as therapeutic. However, as indicated above, the manifestations of fatigue are different from the feeling of suffering or pain considered by the aforementioned decision.

4.3 Moreover, as set out in decision T 655/94 (11 February 1997, to be published in the OJ EPO) a method for treating the human or animal body, though technical, is nevertheless excluded from patentability pursuant to Article 52(4) EPC in view of the high risk for the patient's health involved in one essential part of said method. The reduction in the perception of fatigue does not appear to entail the same considerations since it does not apparently increase

the risk of causing an injury in the muscle tissue. In fact, as stressed by the expert accompanying the appellant's representative at the oral proceedings, no evident relationship exists between the increase of endurance in the muscular system of a fit person performing major exercise and the occurrence of a muscle injury. The expert argued that the gap between the situation of reduced perception of fatigue and the situation in which the muscle tissue may become prone to damage as a result of excessive effort remains very broad and controllable, even after administration of choline. As a matter of fact, no evidence of any injuries was detected during the trials on runners, swimmers and basketball players. The board does not see any reason to question the appellant's arguments, which are therefore accepted.

4.4 On the other hand, it is known from the documents cited during the proceedings before the examining division that choline, or its derivatives which release choline *in vivo*, exhibit a therapeutically relevant activity. Therefore a further question to be considered is whether the non-therapeutic effect according to the application at issue is distinguishable from the therapeutic effect of choline or, on the contrary, whether it is inextricably linked to said therapeutic effect. In the latter situation, the claim would necessarily include a therapeutic treatment as well and would be excluded from patentability in its entirety by virtue of Article 52(4) EPC as already set out in equivalent cases such as decisions T 290/86 (OJ EPO 1992, 414) or T 780/89 (OJ EPO, 1993, 440).

It is the board's view that the two effects of choline are not inseparably linked or correlated but, on the contrary, are readily distinguishable because they involve groups of persons (or patients) undoubtedly distinct. The one consists of patients known to have a

muscular disease, muscular injury or epilepsy, whereas the second comprises healthy persons who will receive no therapeutic benefit from the treatment. Moreover, the times necessary for appreciating the different effects (days for the therapeutic effect and minutes or hours for the non-therapeutic effect) would appear to be so different that no unwanted overlap of the treatment could occur.

Summing up the above arguments, the board's judgement is that claim 1 is directed to a non-therapeutic method.

5. *Novelty*

5.1 As already seen, the first use of choline, in the therapeutic field, is known from documents (1) and (2).

Document (1) discloses the effect of large doses of oral choline on medically intractable human complex partial seizure (CPS). The increase in plasma choline concentration was associated in three patients with a shorter duration of CPS, less post-seizure fatigue and a slight increase in seizure frequency (see page 1336, lefthand column, under "Discussion").

The skilled person faced by the teaching in (1) would not read the less post-seizure fatigue as an aspect independent of the attenuated severity and shorter duration of the individual seizure. In fact, no part of the article lets the reader conclude that choline exhibits a direct effect on post-seizure fatigue or any effect at all outside the pathological picture of epilepsy. The authors themselves underline that the question whether the beneficial actions of oral choline represent a placebo effect or investigator bias remains to be determined. A double-blind prospective study is said to be necessary in order to answer this question.

For these reasons, document (1) does not anticipate the use of choline according to the present application.

Document (2) discloses the use of choline or methionine as methylating agents in the treatment of muscle diseases such as strained or pulled muscles, muscle fibre rupture or sprain, muscle stiffening within the meaning of myogelosis or myalgia. The prophylactic treatment of muscle rheumatism or muscle disorders due to thyroidal diseases is also envisaged.

Although some of the muscle troubles considered in (2), for instance the muscle stiffening, may accompany a state of fatigue, they are independent of it and all remain pathological states caused by a multiplicity of factors, which are not or not necessarily of a physical nature as an excessive physical effort could be (see page 2, second and third paragraph). Thus, though they may occur concomitantly with the perception of fatigue, they cannot be identified with the fatigue itself, which is a non-pathological, natural consequence of the exercise. Therefore, (2) does not anticipate the choline effect according to the application under appeal.

Summing up, the ability of choline to reduce the perception of fatigue is not made available to the public.

5.2 In decision G 2/88 (OJ EPO, 1990, 93, point 10.3 of the Reasons), the Enlarged Board of Appeal set out that a new use of a known compound may reflect a newly discovered technical effect. The attaining of such a technical effect should then be considered as a functional technical feature of the claim seeking protection for such a use. If that technical feature has not been previously made available to the public, the claimed invention is novel, even though such

technical effect may have inherently taken place in the course of carrying out what has previously been made available to the public.

However, an independent invention may be based on the newly discovered effect if such an effect leads to a new technical application which is clearly distinguishable from the previous known application. This is indeed the present case. The prior art documents (1) and (2) describe the use of choline on groups of patients having manifest diseases: either epilepsy or muscle diseases and injuries. Likewise in the case of the prophylactic use of choline envisaged in (2) for muscle rheumatism or muscle troubles arising from thyroidal diseases, the prophylaxis does not appear to mean the prevention of the disease itself, but simply the prevention of the acute phase of a chronic disease. As seen above, fatigue arising from major exercise is not of a pathological nature and the performance itself of major exercise would appear to be quite incompatible with the situations envisaged in the prior art documents, specifically that of muscle injuries. Therefore the non therapeutic use of choline according to the present invention is independent of and distinguishable from the known therapeutic use because it is directed to a distinct group of persons.

For all these reasons, it is the board's judgement that the subject matter of claim 1 is novel.

6. *Inventive step*

6.1 Both the appellants and the examining division have identified in document (2) the closest prior art. The board shares this opinion.

6.2 The underlying technical problem identified in relation to document (2) is to provide new aplications for choline or choline-derivatives which release choline upon administration.

6.3 The solution proposed by the application at issue is the use of choline or a choline derivative for increasing the acetylcholine level in brain and tissue and thereby reducing the perception of fatigue in a person about to participate in major exercise or having completed major exercise.

6.4 The results of the tests carried out on runners, basketball players and swimmers, submitted by the appellants during the proceedings before the examining division and during the appeal proceedings prove that, in all these categories of physical performance, the vigour during the performance was statistically increased compared with the control group and the level of fatigue statistically decreased. For this reason the board is satisfied that the use according to claim 1 actually solves the above-identified technical problem.

6.5 The closest prior art teaches the healing activity of choline or methionine on different muscular diseases or injuries resulting from a multiplicity of situations all apparently characterised by a deficit of adenosine-triphosphate (ATP) in the muscular tissue. The two substances, which act as methylating agents, are said to improve the synthesis of creatine from guanidine acetic acid, thereby facilitating the regeneration of creatine phosphate and the ATP stores in the muscle tissue (see page 5, third paragraph). These effects would appear to lie at the basis of the therapeutic activity of choline and methionine. According to the table on page 9, this activity is monitored as relief of the patient's pain after treatment lasting a few days.

The skilled person called upon to solve the aforementioned technical problem would find no teaching or suggestion in the content of document (2) that the administration of choline would imply any additional therapeutic or non-therapeutic effect in other completely different situations, for instance on healthy persons performing major exercise. Although restoring and maintaining the available ATP play a decisive role in many metabolic processes, including those leading to the manifestation of the perception of fatigue, the skilled man would understand from the teaching in (2) that the final effect of choline on said processes was only detectable in the long term (ie after treatment lasting several days). Therefore he would not expect any effect capable of being appreciated in the short term, ie minutes or hours, as shown by the tests submitted by the appellants. Should the reader of (2) nevertheless have envisaged any relationship between the healing of muscle tissue and the perception of fatigue, he would not have underscored the fact that fatigue is a complex phenomenon resulting from the contribution of many and different factors and processes. These processes occur and terminate within different periods of time, have different limiting agents and probably a different and unpredictable sensitivity to the administration of exogenous agents. For instance among the different steps leading, during physical exercise, to the perception of fatigue, the depletion of ATP and creatinephosphate stores in the muscle tissue is observed within the first few seconds, the anaerobic oxidation of glucose with concomitant accumulation of lactic acid is observed within a few minutes while the aerobic or aerobic/anaerobic mixed processes run for hours. Nothing in (2) would suggest or justify the reasonable expectation that the administration of choline would be able to significantly influence the above seen metabolic processes with the result of

causing a detectable effect at all. Still less, that this detectable effect would be that of reducing the perception of fatigue on the short term as proved with the tests submitted by the appellants.

6.7 The man skilled in the art could not find any better support for the solution of the technical problem in document (1). It is the teaching of (1) that the oral administration of massive amounts of choline during a period of 4 months on medically intractable human complex partial seizures was associated with shorter duration and attenuated severity of the individual seizures, with a slight increase in the seizure frequency and with less post-seizure fatigue. The skilled person would most likely construe the teaching in (1) in the sense that choline exhibits a direct effect on the disease at the level of the central nervous system, ie the origin of the seizure manifestations, and that the reduction in post-seizure fatigue would be the consequence of the reduced duration and severity of manifestations of the disease.

In other words, (1) discloses the ability of choline to reduce the "vigour" of a physical effort, namely the tonic convulsions and muscular contractions typical of human complex partial seizures, thereby reducing post-seizure fatigue. This effect would appear to be just the opposite of the effect achieved by the invention in the application at issue, which seeks the reduction of the perception of fatigue in order to enable the increase or maintenance of vigour during the exercise.

Therefore, in the board's view, the skilled person could not find in this document any suggestion that choline would exhibit any effect at all outside the pathological picture of human epilepsy. Still less that

choline would have a direct effect on the perception of fatigue in healthy persons voluntarily performing major exercise.

Since the clinical pictures disclosed in documents (1) and (2) are dramatically different the one from the other, no combination of their teaching could have been envisaged by the skilled person in the attempt to provide a solution to the above defined technical problem.

6.8 In conclusion, it is the board's judgement that the use of choline according to claim 1 is not obviously derivable from the teaching in the prior art documents and it therefore involves an inventive step. For the same reason, the use of any choline-compound, which derives its activity from the capability of releasing in vivo the free choline, is equally regarded as involving an inventive step.

6.9 Claims 2 and 3 are dependent on claim 1. Novelty and inventive step is acknowledged for the same reasons as given for claim 1.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent with the following claims and a description to be adapted:

claims 1 to 3 according to the main request.

The Registrar: The Chairman:

E. Görgmaier P. A. M. Lançon

Beglaubigt/Certified Geschäftsstelle Registry/Greffe
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München/Munich 03. SEP. 1997