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D E C I S I O N
of 30 September 1997

Case Number: T 0521/94 - 3.3.4

Application Number: 85114699.3

Publication Number: 0182356

IPC: A23L 1/305

Language of the proceedings: EN

Title of invention:
Nutrient compositions

Patentee:
The Montefiore Hospital Assocation of Western Pennsylvania, et al

Opponent:
Fresenius AG

Headword:
Nutrient compositions/MONTEFIORE HOSPITAL

Relevant legal provisions:
EPC Art. 56, 54

Keyword:
"Inventive step - yes"
"Novelty - not a ground of the opposition"

Decisions cited:
G 0007/95

Catchword:
-

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Case Number: T 0521/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 30 September 1997

Appellant: (Opponent)
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Respondent: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 20 April 1994 concerning maintenance of European patent No. 0 182 356 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: D. D. Harkness
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 182 356 relating to "Nutrient compositions" was granted with 12 claims on the basis of patent application No. 85 114 699.3. Independent claims 1, 8 and 10 read as follows;

"1. A nutrient composition comprising an aqueous solution containing from 0.2 to 40 weight percent of protein nutrients including 0.2 to 30 weight percent of oligopeptides consisting of dipeptides and tripeptides wherein at least one said oligopeptide contains a glycine residue as the N-terminal amino acid residue; and

at least one said oligopeptide contains as the N-terminal amino acid residue an amino acid residue selected from the class consisting of alanine, lysine and arginine.

8. A nutrient composition comprising dipeptides of L-threonine, L-valine, L-methionine, L-isoleucine, L-leucine, L-lysine, L-tryptophan, L-histidine, L-phenylalanine, L-glutamic acid, L-proline, L-glutamine, L-alanine and L-tyrosine, and, as the N-terminal residue of at least one of said dipeptides, a glycine residue and, as the N-terminal residue of at least one of said dipeptides, at least one other amino acid residue selected from the class consisting of L-alanine, L-lysine and L-arginine."

II. An opposition was filed based on Article 100(a) EPC on the ground that the subject-matter of the claims did not comply with Article 56 EPC.

III. On 20 April 1994 the opposition division issued a decision whereby the patent was maintained in amended form in accordance with Article 102(3) EPC, whereby the

amendment was that independent claim 10 was made dependent upon claim 1.

IV. The opposition division stated that the amendments made in the description and claims did not contravene Article 123(2) and (3) EPC. Further the prior art did not contain any disclosure which was detrimental to the novelty and inventive step (Articles 54 and 56 EPC).

V. The Appellant (Opponent) lodged an appeal in due time against the decision of the opposition division and filed with the statement of grounds a new schedule of prior art citations B1 to B16 of which B1, B10, B11, B13 and B14 were newly filed documents.

VI. In the answer to the grounds for appeal the Respondent argued that the late filed documents be disregarded by the Board under Article 114(2) EPC.

VII. Oral proceedings were held on 30 September 1997. The Respondent filed a new main request and an auxiliary request. Claim 1 of the main request reads as follows:

"1. A parenteral nutrient composition comprising an aqueous solution containing from 10 to 40 weight percent of protein nutrients including 2 to 20 weight percent of oligopeptides consisting of dipeptides and tripeptides wherein at least one said oligopeptide contains a glycine residue as the N-terminal amino acid residue;
and
at least one said oligopeptide contains as the N-terminal amino acid residue an amino acid residue selected from the class consisting of alanine, lysine and arginine."

In the oral proceedings the parties relied on the following documents:

(B1) DE-OS 2 260 189

(B2) EP-0 087 750

(B3) DE-OS 3 108 079 A1

(B4) Infusionstherapie 12, (1985), S. 70-76

(B5) Akt. Ernährung. 4 (1979), S. 173-177

(B6) J.Nutr. 108 (1978), S. 1104-113

(B7) The Am. Journal of Clinical Nutrition 29 (1976), S. 205-215

(B14) Defined Formula Diets For Medical Purposes, (1977), S. 15-24 (American Medical Association, Chicago, I11.)

Further, claim 8 was made dependent on claim 1 and claims 9 to 11 were cancelled.

VIII. The submissions of the Appellant are summarised as follows:

Novelty objections were newly raised based on documents B1 and B2.

The inventive step of the claimed subject-matter was attacked using document B3 as the nearest prior art in combination with other references in the citations.

Citation B3 disclosed that the problem of providing a nutrient composition from which the aminoacid content would be easily assimilated by people and young animals

and also hypertonicity would be avoided, was solved by an aqueous oligopeptide nutrient composition containing at least two different di- and/or tri-peptides each one having a terminal N-glycine residue.

In the light of this disclosure the problem to be solved by the patent in suit was that of providing an alternative and improved nutrient composition.

From document B3 it was obvious to use in nutrient compositions oligopeptides which had terminal N-glycine residues as required by the claims of the patent in suit, and it was obvious from B5 that glycine was employed with other aminoacids and that parenteral use of too much glycine in nutrients gave rise to toxicity problems. It was also known from B3 that oligopeptides having terminal N-glycine residues were especially water-soluble and could be used in high concentrations. Furthermore these oligopeptides were taken up more readily by the body cells in a none-hydrolysed state and only in the body cells did splitting into the separate aminoacids take place.

The language of claim 9 of document B1 was that more than one tyrosine-dipeptide could be combined with the branched-chain amino acids of the aqueous injectable composition there referred to.

Tyrosine dipeptides were the subject of document B6 which examined their solubility in comparison with that of tyrosine. The conclusion was that alanyl-tyrosine is rapidly metabolised when administered as part of a parenteral alimentation solution and that this depended upon uptake of intact peptide into the body tissue with subsequent intracellular hydrolysis. This result was stated to be similar to that obtained by Adibi et al in their studies of glycyl-leucine published in Clin.Sci. and Mol. Med. 52. 193-213.

Further, it was obvious from document B7 page 209 first paragraph that a number of dipeptides were suitable for use in humans including glycyl-leucine, alanyl-glycine, arginyl-leucine and leucyl-leucine, which were all presented as alternatives and if it were necessary to replace dipeptides of glycine then it was obvious to employ those mentioned not having glycine as a constituent.

Amounts of the oligopeptides in the claimed compositions were conventional, 40% of aminoacids was specified in claim 1 of document B1 and in particular 4 to 10% was quoted in claim 11. Di- and tri-peptides of glutamine were present in amounts of 1 to 50g per litre of aqueous composition in document B2, whilst document B3 disclosed 1 to 20% by weight. Further high concentrations of oligopeptide (50-100 mM) were suggested by B14 for use in the intestinal lumen.

The subject-matter of the patent in suit could not be regarded as a selection invention nor was there any evidence of a synergistic effect as a result of the combination of components in the claimed composition.

IX. The Respondent's submissions are summarized as follows:

The claimed subject-matter was novel.

The disclosure of document B1 was not relevant to inventive step because there was no reference to a mixture of di-or tri-peptides. The language of claim 9 of this document was in the singular and not in the plural and this was borne out by the last paragraph on page 29 where alternatives were given.

Independently of what the objective problem vis-à-vis the nearest prior art may be said to be, there was an unexpected advantage resulting from the claimed subject-matter. This resided in the fact that the food assimilation efficiency in terms of the utilisation of the oligomers was exceptionally high as exemplified by the 1% figure for urinary excretion of peptides of Table 2 of the patent in suit in comparison with the 6% quoted in document B6 at page 1111 right hand column. Figures of 3% or more were not acceptable. Further this was achieved whilst employing up to 40% by weight of protein nutrients. Such efficiency was not realisable using simply any combination of aminoacids and di- or tri-oligopeptides. It was important that the glycine oligopeptides were present in combination with the oligopeptides of alanine, lysine and arginine, other combinations would not necessarily be successful.

The prior art did not suggest to the skilled person that a combination of glycine oligopeptides with those now proposed would lead to the advantages outlined above.

In particular document B1 did not refer to mixtures of oligopeptides and therefore was not relevant for obviousness purposes.

The disclosure of document B3 constituted the nearest prior art but this had no relevance to mixtures containing oligopeptides other than those of glycine and there was no pointer to the problem to be solved.

Document B4 at pages 72 and 73 had nothing to do with the subject-matter now claimed as the recommendations were that three other components, cystein, tyrosin and glutamin, were essential for intravenous use.

Document B5 only indicated that a high level of glycine in nutrient compositions should not be encouraged and in other respects it was irrelevant.

The study of tyrosine in document B6 represented a subject remote from that of the patent in suit and was not at all concerned with glycine oligopeptides. There was no reason to combine the teachings of documents B3 and B6 because B3 had no starting point from which it was possible to link up with B6 which related to a study of the none-essential aminoacid tyrosine and peptides thereof.

Document B7 disclosed nothing which was relevant because it only discussed the absorption in man of various dipeptides without further disclosures directly pertinent to the patent in suit.

The disclosure in B14 at page 23 that high concentrations of oligopeptides could be employed in the intestinal lumen in humans was not of any significance for inventive step of the claimed subject-matter.

Document B15 concerned only general disclosure in relation to peptides and was therefore not relevant to the specific details of the patent in suit.

X. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the auxiliary request submitted at the oral proceedings on 30 September 1997.

Reasons for the Decision

Main request

1. *Amendments, Article 123(2) and (3) EPC*

The amendments made to the description and the claims resulting in the main request do not give rise to objection under this article as they are all of a limiting nature, are based upon the original disclosure and do not extend the scope of the claims beyond that of the claims as granted. There were no objections expressed by the Appellant in respect of the amendments made during the oral proceedings.

2. *Late filed documents, Article 114(2) EPC*

Of the documents filed outside the nine month period for opposition B10, B11 and B13 were not admitted into the proceedings as they were no more relevant for the determination of inventive step than those filed in time.

3. *Novelty, Article 54 EPC*

Although the opposition division gave an opinion in respect of novelty and decided in favour of the Respondent, this ground of opposition did not form part of the opposition as filed. Since the Respondent had previously refused to accept further grounds of opposition in his letter dated 6 March 1995, part III paragraph 1, and did not tender any agreement during the oral proceedings to the introduction of such a new ground for opposition, said ground was not accepted by the Board as part of the proceedings (see Enlarged Board of Appeal decision and G 7/95 (OJ EPO 1996, 626 see reasons at paragraph 7.1).

4. *Inventive step, Article 56 EPC*

4.1 The closest prior art

The parties and the Board agreed that document B3 represented the nearest prior art for the determination of inventive step. This document disclosed aqueous nutrient compositions containing at least two different di- and/or tri-peptides each one having a single terminal N-glycine residue. One to 20% by weight of these peptides may be present in an aqueous solution suitable for parenteral application.

4.2 The technical problem

In the light of the nearest prior art the problem to be solved resides in the provision of an alternative aqueous di- and/or tri-oligopeptide protein nutrient composition in which the oligopeptides exhibit an N-terminal glycine residue.

4.3 The solution to the problem

The problem was solved by the provision of protein nutrient compositions as claimed in claim 1 of the main request.

4.4 Assessment of inventive step

4.4.1 The differences between the composition of document B3 and that of the patent in suit is a combination of an oligopeptide having a terminal N-glycine residue and at least one oligopeptide containing as the N-terminal aminoacid residue a residue selected from alanine, lysine and arginine. This mixture of oligopeptides is further characterised by the given proportions by weight.

4.4.2 The oligopeptides disclosed in document B3 all contain an N-terminal glycine residue, and such oligopeptides were employed to overcome the problem of hypertonicity. The disclosure does not refer to any oligopeptides of alanine, lysine and arginine as additives to the compositions there described. Advantages put forward by the Respondent for the claimed compositions are that toxicity due to the presence of glycine resulting from hydrolysis is low and that the protein nutrients are efficiently absorbed by the patients. Such advantages are not derivable from B3 in an obvious manner. The question is whether a combination of document B3 with any other document would lead the skilled person in an obvious manner to the claimed subject-matter.

4.4.3 Chronologically document B3 was published after documents B5 and B6. Therefore the inventor and skilled person who provided the compositions of B3 did so in the knowledge of documents B5 and B6.

4.4.4 In spite of the warning issued in B5 not to increase levels of glycine through parenteral feeding, the inventor of B3 provided compositions which contained only oligopeptides having N-terminal glycine residues thus increasing the possibility that glycine would be produced by hydrolysis. Accordingly the teaching of these two documents would appear to be contradictory and no proper combination of their teaching can be made.

4.4.5 Document B6 recognised that tyrosine was an essential aminoacid for infants, however this aminoacid is of limited solubility and a study revealed that in oligopeptide form tyrosine was more soluble and therefore more readily available for absorption by the patient. Consequently tyrosine in the form of alanyl-tyrosine di-peptide was recommended for parenteral alimentation solutions, see the discussion on

page 1108. Again the inventor of B3 did not take up this suggestion already known to him. There is no real link between documents B3 and B6 when starting from B3 because this citation does not suggest any oligopeptides other than those having a terminal N-glycine residue and B6 whilst investigating the solubility of tyrosine oligopeptides does not have an undeniable connection with the specific protein nutrient compositions of B3 and certainly not in the specified proportions of the compositions of claim 1 of the patent in suit. The disclosure in B6 (page 1111 right hand column) that the excretion of free alanine and alanyl-tyrosine from rats indicated a 6% loss of nutrients does not in any way encourage the skilled person to use said peptides or how to achieve a loss of only 1%. The combination of the two kinds of oligopeptides defined in the main claim in the amounts specified do enable such a result to be achieved and this was not foreseeable from the prior art.

4.4.6 There is no combination of any one or more of documents B1, B2, B7 or B14 with B3 which leads to the provision of protein nutrient compositions as claimed, nor is the combination of the two advantages of reduced toxicity due to glycine content resulting from hydrolysis and that of reduced loss of protein obviously derivable from them for the following reasons:

Document B1 does not contain such language in its claim 9 as to suggest that more than one oligopeptide is present in the compositions claimed and the general disclosure is that only compositions containing one oligopeptide are described. The paragraph following Table 7 relates only to alternative oligopeptides and not to combinations.

The disclosure of document B2 is concerned with the use of di- or tri- peptides of glutamine having an aminoacyl residue in order to overcome a toxicity problem. The examples do not provide a composition containing the two types of oligopeptides which characterise claim 1 of the patent in suit. Further the combination cited by the appellant (column 2, line 48) is not a true combination because the peptides quoted are alternatives each of which contains the glutamin residue which in this form is non-toxic. Also the highest concentration of protein nutrients disclosed (see Example 1) is approximately 7,5% by weight and this is below the minimum required by the Respondent's claim.

Document B7 discusses the intestinal assimilation of proteins and in conclusion makes a general statement that because of greater absorption rates of aminoacids when introduced in the form of di- and tri-peptides instead of free aminoacid mixtures then these peptides may be useful in nutritional therapy. The listed peptides include peptides of both kinds necessary for claim 1, however, there is no reason whatsoever to choose such a combination, particularly since document B3 only refers to peptides having a terminal N-glycine residue.

The reference in document B14 at page 23 to the use of high concentrations of oligopeptide in the intestinal lumen (50-100 mM) is not transferable to an aqueous composition suitable for parenteral applications. This document is concerned with a study of the intestinal absorption of oligopeptides which has no bearing upon the problem solved by the claim 1 of the patent in suit, which relates to parenteral nutrient compositions. It is also said that a peptide which has

a bulky N-terminal amino acid residue is likely to be hydrolysed by enzymes before being taken up in the form of a di- or oligo-peptide. This evidence would militate against preparation of the protein nutrient compositions as claimed.

For the above reasons the subject-matter of claim 1 of the main request is considered to comply with the requirements of Article 56 EPC. Since all of the subsidiary claims are dependent on claim 1 their subject-matter is also inventive.

Auxiliary request

In these circumstances the auxiliary request is not to be considered.

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 maintain the patent on the basis of the claims submitted as main request on 30 September 1997 and the amended description submitted on 30 September 1997.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey