BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File Number: T 482/90 - 3.3.2

Application No.: 85 304 685.2

Publication No.: 0 167 381

Title of invention: Increasing the efficiency of poultry production

Classification: A61K 37/43

D E C I S I O N
of 17 October 1990

Applicant: Embrex, Inc.

Headword: Poultry production/EMBREX

EPC Articles 54 and 56

Keyword: "Novelty (yes), Inventive step (no)" - "Obvious application of scientific knowledge in an industrial process"

Headnote

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 482/90 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 October 1990

Appellant : Embrex, Inc.
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Decision under appeal : Decision of Examining Division 001 of the European Patent Office dated 29 January 1990 refusing European patent application No. 85 304 685.2 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P.A.M. Lançon
Members : U. Kinkeldey
R. Schulte

Summary of Facts and Submissions

I. European patent application No. 85 304 685.2, published as No. 0 167 381, was refused by the Examining Division. The application as refused had twenty claims. The independent Claims 1, 3 and 9 related to a method of increasing the efficiency of poultry production by treating the embryo (Claim 1), poultry eggs (Claim 3) or turkey eggs (Claim 9).

Independent Claim 11 reads as follows:

11. Use of a thyroid hormone, a thyroid hormone precursor or a neuroendocrine thyroid regulator hormone for the manufacture of a formulation for treatment of a poultry embryo of a poultry strain of known reduced hatchability in ovo during late embryonic development to augment the endogenous thyroid output of the embryo by the administration of said thyroid hormone, thyroid hormone precursor or neuroendocrine thyroid regulator hormone in a dosage which is a physiological dosage, such as to reduce the embryo mortality rate.

II. The grounds given for refusal were that the application did not meet the requirements of Articles 52(4), 54 and 56 EPC. The main arguments were as follows:

(a) Methods as claimed in Claims 1 to 10 were clearly methods for treatment of the animal body by therapy. An unhatched embryo was considered to be an animal body. Further, a hypothyroid hormone level which led to high mortality was considered to be a disease which required treatment by therapy.

(b) Remaining Claims 11 to 20 did not involve an inventive step as required by Article 56 EPC in the light of the following prior art documents:

(1) Comp. Biochem. Physiol., Vol. 75A, No. 3, 1983, pages 379-384. J. Wittman et al. "Motility pattern and lung respiration of embryonic chicks under the influence of L-thyroxine and thiourea";

(2) J.F. Zilva, PR Dannall; Clinical Chemistry in Diagnosis and Treatment 3rd ed, London 1981, page 161.

From document (1) it was known that L-thyroxine (T_4) had an accelerating effect on hatching. Although said document did not reveal the mortality of the embryos of thyroxine-injected eggs, there was no doubt that the mortality was, in fact, decreased. Therefore, the use of thyroxine for the treatment of poultry eggs, which led necessarily to an increase of the efficiency of poultry production by decreasing the mortality, was not novel. Accordingly, Claim 11 was not allowable according to Article 54 EPC.

(c) Claims 12 to 20, which defined specific embodiments of Claim 11, were formally novel. However, with regard to the prior art document (1), no inventive step could be seen in the use of thyroid release hormone (TRH), thyroid stimulating hormone (TSH), triiodo-thyronine (T_3), thyroid hormone precursors or other thyroid hormones as well as neuroendocrine thyroid regulator hormones for the present purpose, since it was well known that these compounds had essentially the same effects as L-thyroxine, or that

they increased in one way or another the natural thyroxine-production. This view was also supported by document (2).

III. The Appellants appealed against the decision to refuse their application.

IV. With the Statement of Grounds the Appellants cancelled Claims 1 to 10 and thus Claims 11 to 20 form the basis for the appeal.

The Appellants' arguments may be summarised as follows:

(a) Regarding Article 54 EPC:

Claim 11 specified that the thyroid hormone etc. was administered in a physiological dosage. The term was defined as being on the order of the normal level of the substance found in healthy eggs. According to the present invention, 50 nanograms of T_4 per egg were administered, compared to a normal level of about 22-73 nanograms in a healthy embryo. In contrast, document (1) taught the administration of a dose of 14 683 nanograms per egg, which was far in excess of what might reasonably be termed as a physiological dosage. In fact, the dosage disclosed in document (1) was an approximately lethal dosage. Claim 11 was thus novel.

(b) Regarding Article 56 EPC:

The subject-matter of the invention as now claimed in Claims 11 to 20 was also inventive. With regard to document (1) it was submitted that firstly the disclosure of this document was concerned with speeding up hatching whereas the present invention was concerned with improving success rate, which were

two quite unrelated effects. Secondly, a man skilled in the art reading document (1) would have understood that the observed effects were restricted to the approximate dosage regimes used by the authors of document (1) and could not meaningfully be extrapolated outside those regimes. In support of these arguments, attention was drawn to three further documents:

(3) V.W. Hylka et al. Comp. Biochem. Physiol. 84a, 275 (1986)

(4) A.L. Romanoff, "Biochemistry of the Avian Embryo", Interscience Publishers, John Wiley and Sons, New York, London, Sydney (1967)

(5) G.J. Wishart et al. Gen. Comp. Endocrinol. 31, 373 (1977).

In contrast to the disclosure of document (1) the present application taught the injection of an amount of the respective substances mentioned in Claim 11 being in the same range as the fluctuation of endogenous T_4 seen in chicks during the last quarter of incubation. It beared note that T_4 powerfully stimulated metabolic activity. Thus, the doses taught by document (1) for example either massively stimulated metabolic activity in the embryonic chick or inhibited metabolic activity through down-regulation ("paradoxical inhibition"). Thus, nothing in the literature suggested why one seeking to solve the problem of late embryonic mortality in poultry would look to a paper studying the ability of a lethal-level T_4 dose to stimulate hatching. It was the applicant's contribution that a low dose T_4 will solve this problem.

The know: physiology of chick development also s ported the foregoing contention. The parafetal development of a chick embryo was highlighted by (a) internal pipping, then (b) external pipping and then (c) hatching. Disruption of these events would be harmful to the chick: Document (1) demonstrated that administration of T_4 caused premature yolk sack retraction, the yolk sack providing food for the chick prior to hatch and for a short time after hatch and resulted in increased mortality. Thus, there was no logical or actual correlation between speed of hatching and percentage mortality. The present invention showed that mortality rates were actually decreased by administering physiological dose which was not suggested in any of the prior art documents.

As to the inventive step of Claim 12, which related to substances selected from the group consisting of thyroid release hormone (TRH), thyroxine (T_4), Triiodothyronine (T_3), thyroid stimulating hormone (TSH) and tyrosine, it was submitted that only if the physiological mechanisms of said substances were known could one have extrapolated from the effects of the substance as claimed in Claim 11. In the present case, no such mechanism was known prior to the present invention and thus it was the inventors having actually conducted experiments and found that these substances had shown the effect justifying an inventive step.

IV. During oral proceedings which took place on 17 October 1990 the Board drew attention to a further prior art document cited in the Search Report, namely

(6) Christensen et al. "Physiology of turkey embryos during pipping and hatching. IV. Thyroid function in embryos from selected hens", Poultry Science No. 61; pages 2482 to 2488 (1982).

There, clearly a relationship between hyperthyroidism and high hatchability and evidence that thyroid hormones may be the "hatching response" stimulus in incubating turkey embryos was disclosed.

It was emphasised by the Appellants that any scientific knowledge about correlations between the level of any thyroid hormones and hatchability was not suited to use said hormones in a physiological dose in an industrial process with the effect of a decrease of mortality.

V. The Appellants requested that the decision under appeal be set aside and a patent be granted on the basis of Claims 11 to 20 as rejected by the Examining Division.

Reasons for the Decision

1. The appeal is admissible.

2. Since the Appellants cancelled Claims 1 to 10 during the appeal procedure the question of patentability with regard to Article 52(4) EPC is no longer at issue.

3. **Novelty (Article 54 EPC)**

Claim 11 was rejected by the Examining Division as being not novel over document (1). In the Board's opinion the argument put forward by the Appellants in their grounds of the appeal, namely that the dosage administered in

document (1) was lethal, whereas the dosage mentioned in Claim 11 was physiological, is convincing. Claim 11 is thus novel over document (1). No other cited prior art document comes closer than document (1) and thus novelty cannot be questioned by these documents either.

4. Inventive step (Article 56 EPC)

The issue to be dealt with is now whether the subject-matter of Claim 11 involves an inventive step as required by Article 56 EPC.

Claim 11 relates to the use of a thyroid hormone, a thyroid hormone precursor or a neuroendocrine thyroid regulator hormone for the manufacture of a formulation for treatment of a poultry embryo of a poultry strain of known reduced hatchability in ovo during late embryonic development to augment the endogenous thyroid output of the embryo.

5. The closest state of the art is document (1), which relates to the administration of a thyroid hormone, namely L-thyroxine into eggs from brown Leghorn hens in order to study the influence of thyroid hormones on the mortality and respiratory behaviour of the embryos, the administration carried out on day 17 of incubation. The thyroid hormone is administered in an amount of 18.9 nmol. It was observed that the injection of L-thyroxine induced an onset of lung respiration about twenty hours earlier than normal (page 381, right column, paragraph 3 and Figure 4). Furthermore, the phase of reduced activity also started earlier. In L-thyroxine-treated chicks metabolic parameters were changed and the hatching process was accelerated as well (page 382, right column, first paragraph). Due to the known stimulatory effects of L-thyroxine it is assumed that, compared with controls, the

developmental stage enabling the lungs to take over the respiratory function is reached earlier than normal under the influence of L-thyroxine. Document (1) further suggests that lung respiration represents a prerequisite for a better O_2 supply by which increased energy, needed for the hatching process, is produced. In conclusion, the experiments provided in document (1) indicate a premature onset of lung respiration of embryonic chicks under the influence of exogenous L-thyroxine. It is assumed that the premature onset of lung respiration accelerates the increase of the ratio of CO_2 and O_2 tension in the air cell, which represents a stimulus for the hatching process (page 384, left column, last paragraph).

6. Starting from document (1), the problem underlying the patent application can be seen in improving the process of document (1) for the industrial application in poultry production.

7. This problem is solved in the patent application as described in Claim 11 by the administration of the thyroid hormone, thyroid hormone precursor or neuroendocrine thyroid regulator hormone in a dosage which is a physiological dosage, such as to reduce the embryo mortality rate. The data given in Tables I to V show that the hatchability actually is increased and thus that the problem is solved.

8. The question is whether, starting from document (1), it was obvious to a skilled person, based on the knowledge disclosed in said document about the effect of L-thyroxine, to use the method of injecting eggs on specific days with a thyroid hormone in a physiological dosage to reduce the embryo mortality rate and thus to increase the efficiency of the production of poultry.

9. When answering this question one has to bear in mind what is stated in the description of the present patent application, which corresponds to and confirms what is disclosed in document (1) and thus forms common general knowledge, as the actual reasons for carrying out the method as claimed in Claim 11. This is: "The intense genetic selection of turkeys, chickens and other poultry has achieved dramatic increases in body size and growth rate. However, it is well known that genetic selection has adversely affected the efficiency of poultry production by causing alarmingly low average hatchability rates for the eggs, as low as about 70% for many strains of domestic turkeys. Current efforts made up to optimise the hatchability of poultry eggs have centered primarily on optimising controlled environmental conditions (e.g. temperature, humidity und gas concentration) for egg incubation. Other steps, including the injection of antibiotics at different stages of incubation, have been used to control disease". According to the description it was known that in wild species there existed a delicate balance between the functional gas conductance properties of the eggshell and the supply of vital gases to an increasing tissue mass. It was observed that "the genetic selection of domestic poultry had caused a dissynchronous relationship between functional eggshell properties and the O_2, CO_2 and water vapour requirements of the embryos". Therefore, apparently, while the intense genetic selection of poultry certainly had important advantages, it was apparently connected with the mentioned disadvantages. It is further stated in the introductory part of the present patent application that "experimental data had indicated that thyroid hormones play an important physiological role in the successful hatching of domestic poultry, for example that plasma thyroxine (T_4) concentrations appear to be significantly greater at days 26 and 27 of incubation in so-called high hatchability groups of turkey

eggs. The high hatchability groups also show significantly higher oxygen consumption, indicating a higher metabolism". As becomes clear from the Tables I to V, where the hatchability of treated eggs is compared with respective controls, the treated groups of eggs were those of low hatchability, i.e. showing a percentage of hatchability of at most 74.5% (Table I). It is further clear from the description (page 3, lines 3 to 14) that the intention of the method of Claim 11 was to increase the level of circulating hormone concentration in low hatchability groups to the level found in good hatching embryos.

This knowledge, already presented in the present patent application, together with the clear disclosure in document (1) as already defined above (see point 5 above) clearly shows, that it was common general knowledge that high mortality rate was due to low hatchability.

10. Being equipped with the scientific knowledge about the effect of L-thyroxine on metabolic parameters as well as the hatching process - in particular that the premature onset of lung respiration accelerates the increase of the ratio of CO_2 and O_2 tensions in air cell, which represents a stimulus for the hatching process - it is, in the Board's opinion, obvious for a skilled person to try the administration of a thyroid hormone in a physiological dosage with a reasonable expectation of success.

11. The Appellants argued that one could not have been sure that said success would actually be the result of the claimed method, because one can never be sure that scientific knowledge can reasonably be adapted to an industrial process unless one were able to prove any assumption by actual experiments. These experiments have been carried out by the applicants, who were, thus, the

first to show that experimental knowledge actually worked in an industrial process. Further, document (1) led away from the invention because in this document the eggs were injected with lethal doses of the hormone.

12. The Board is not convinced by these arguments.

It is correct that one cannot be sure whether an experimental result achieved in laboratory work is also applicable in an industrial process. Nevertheless, according to the Board's opinion it is quite a normal step for a skilled person to adapt scientific results for commercial use. If a scientific result is considered to be suitable to solve a given problem, this is in any case, in the Board's opinion, an incentive for the skilled person to put this scientific knowledge into practice, unless there are serious reasons preventing a skilled person from doing so.

13. The disclosure of the administration of a lethal dosage of thyroid hormone in document (1) is interpreted by the Board in quite a different way than it was done by the Appellants. If, as in the present patent application, it is the purpose to decrease late embryonic mortality of poultry eggs, it would seem then to be rather obscure to follow a teaching of administration of a lethal dosage. Since, however, this dosage, which is said to be lethal, was apparently suited to study the correlation between thyroid hormone and hatchability, it seems to be self-evident that the administration of physiological doses in low hatchability groups, which were known to suffer a low thyroid hormone level, increase the hormone level to a normal status and thus increase hatchability and consequently decrease mortality.

14. In document (6), it is also disclosed that hypothyroidism may be a physiological factor limiting hatchability in domestic turkeys (page 2482, Abstract). Further, in particular in the part "Discussion" (page 2486, right column), it is stated that the present study suggested that the metabolism of poult embryos during pipping and hatching differs according to the embryos inherited hatchability. The study implicated that decreased embryonic thyroid function is connected with decreased hatchability in turkeys. Increased body weight increased egg size and incubation time but decreased embryonic metabolism. The selection of domestic turkeys for rapid growth and increased body size might also have resulted in lower metabolic rate in embryos. The study provided evidence that decreased metabolic rate might manifest itself most acutely during pipping and hatching where thyroid secretion is essential for successful emergence from the shell. It is thus suggested that embryonic hypothyroidism might be a limiting physiological factor in hatchability of turkey poults.

15. Also from this document it seems to be clear that non-hatching and thus mortality in poultry eggs is connected to hypothyroidism, i.e. a non-normal and thus "unphysiological" level of thyroid hormone. No inventive effort is, therefore, necessary to increase the level of thyroid hormone at the decisive days of embryonic stage to the normal, and thus "physiological" level. This document also provides information which would have prompted a skilled person to administer a physiological dosage of a thyroid hormone, thyroid hormone precursor or a neuroendocrine thyroid regulator hormone, and in doing so to reasonably expect a success.

16. The prior art documents (3) to (5), which were discussed by the Appellants in their grounds of appeal in support of their arguments that it was not to be expected that the administration of a physiological dosage of a thyroid hormone would have the desired effect of a decrease of mortality of the embryos in a poultry production, do not, in the Board's opinion, provide information which goes beyond that of above discussed documents (1) and (6). Document (3) was published only after the priority date of the present patent application and, thus, apparently was cited by the Appellants to provide post-published evidence that the normal level of two types of a thyroid hormone, T_3 and T_4, show concentrations in the range of 13.8 to 10.8 ng/ml. This concentration range combined with the disclosure given in document (4) gives, according to the Appellant's submissions, total circulating T_4 levels of 22 to 73 ng in a parafetal chicken or turkey. The Appellant's argument was that the dosage in document (1) was lethal, so that, as discussed in detail above, the skilled person would have been prevented from further investigating the use of thyroid hormones in reducing late embryonic mortality in poultry. The Board, however, believes that the disclosure of documents (3) and (4) gives the skilled person a quite different message. Knowing that the normal total circulating T_4 levels in a parafetal chicken or turkey equals 22 to 73 ng it seems to be the obvious step to administer a dosage lying within this range when it is otherwise known that a certain undesired effect is caused by a too low level of this hormone, called hypothyroidism. Document (5) provides evidence that a certain amount of a thyroid hormone is lethal. This document, therefore, is on the same line as document (1).

17. The Appellants emphasised that one cannot compare low hatchability and mortality and, therefore, none of the prior art documents could provide the skilled person with any knowledge that accelerating hatching will solve the problem of late embryonic mortality. It should be abundantly clear from, in particular, document (4) that there was no logical or actual correlation between speed of hatching and percentage mortality, except to the extent that speeding up hatching would be expected to lead to prematurity and an attendant increase in mortality percentages. This argument did not convince the Board, because it seems to be evident that an increase in hatchability does not necessarily mean a premature hatchability. Rather, in correlation to "low hatchability", which certainly does not mean "late" hatchability but rather "no" hatchability in a certain percentage of cases, the increase in hatchability just indicates that a higher percentage of embryos does indeed hatch. Since embryos which cannot hatch for whatever reason will definitely die in their eggshell, it seems to be self-evident that a skilled person will connect high hatchability rates with a decrease of mortality. This view is supported by statements given in the present patent application where it is stated on page 1, lines 20 to 24 that it was known that over 90% of the embryos of domestic turkeys were live at or near days 24 to 25 of incubation, indicating that a very large insignificant number of the embryos that do not hatch die late in incubation.

18. Thus, no inventive effort was necessary to use hormones as mentioned in Claim 11 for the manufacture of a formulation for treatment of poultry embryo of a poultry strain of known reduced hatchability in ovo during late embryonic development in a dosage which is a physiological dosage, so as to reduce the embryo mortality rate.

19. Claims 12 to 20, which are dependent on Claim 11, share the fate of Claim 11, since no arguments were submitted for an unexpected effect of one of the embodiments being different from that described for the subject-matter of Claim 11; nor were requests submitted containing accordingly restricted claims.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: **The Chairman:**

M. Beer **P.A.M. Lançon**