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The opinion in support of the decision being entered today
(1) was not written for publication in a law journal and
(2) is not binding precedent of the Board.

Paper No. 27

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte IRVING BOIME

Appeal No. 95-2613
Application 07/876,794¹

ON BRIEF

Before WILLIAM F. SMITH, **Administrative Patent Judge**, and
FRED E. MCKELVEY, **Senior Administrative Patent Judge**, and
ELLIS, **Administrative Patent Judge**.

ELLIS, **Administrative Patent Judge**.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final
rejection of claims 1 through 4 and 7 through 10, all the
claims remaining in the application.

Claims 1 through 3 and 7 through 9 are illustrative of

¹ Application for patent filed April 30, 1992.

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the subject matter on appeal and read as follows:

1. An improved method for recombinant production of a human gonadotropin, which method comprises culturing animal cells that contain regulated secretory granules and which cells have been transformed with an expression system capable of expressing a DNA encoding said gonadotropin under conditions wherein said encoding DNA is expressed, and

recovering the gonadotropin from the culture medium.

2. The method of claim 1 wherein said cells are pituitary cells.

3. The method of claim 2 wherein said pituitary cells are GH₃ cells.

7. A cell culture capable of secreting a human gonadotropin which cell culture comprises animal cells that contain regulated secretory granules and which cells have been transformed with an expression system capable of expressing a DNA encoding said gonadotropin under conditions wherein said encoding DNA is expressed, and

recovering the gonadotropin from the culture medium.

8. The culture of claim 7 wherein said cells are pituitary cells.

9. The culture of claim 8 wherein said pituitary cells are GH₃ cells.

The references relied on by the examiner are:

Boime
(PCT Application)

WO 90/09800

Sept. 7, 1990

Vander et al. (Vander), **Human Physiology, The Mechanisms of Body Function**, Second Edition, McGraw-Hill, Inc., NY, p. 184

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(1975).

Hellerman et al. (Hellerman), "Secretion of human parathyroid hormone from rat pituitary cells infected with a recombinant retrovirus encoding preproparathyroid hormone", *Proc. Natl. Acad. Sci. USA*, Vol. 81, pp. 5340-5344 (Sept. 1984).

Clayton, et al. (Clayton), "Expression of luteinising hormone-
\$ subunit chloramphenicol acetyltransferase (LH-\$-CAT) fusion gene in rat pituitary cells: induction by cyclic 3'-adenosine monophosphate (cAMP)", *Molecular and Cellular Endocrinology*, Vol. 80, pp. 193-202 (1991).

Claims 1 through 4 and 7 through 10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Boime in view of either Hellerman or Clayton, and Vander.

We **reverse**.

Background

Human reproductive hormones (gonadotropins) are a family of "heterodimeric glycoprotein hormones which have a common " subunit, but [which] differ in their hormone-specific \$ subunits." Specification, p. 1, lines 18-21. The claimed invention is directed to a method of producing human gonadotropins² by culturing regulated secretory granule-

² Human gonadotropins are reproductive hormones which include follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyrotropin or thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (CG).

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containing animal cells which have been transformed with an expression vector which is capable of expressing a DNA sequence encoding a human gonadotropin. The specification states that

Certain cells are known to contain dense-core secretory granules and to secrete proteins through a regulated pathway, which can be stimulated by certain substances, for example, forskolin. These cells or cell lines, derived from appropriate animal tissues, are the host cells of the invention. Included among such cells are cells of the secretory components of the hormone system such as the pituitary, β islet cells, and cells of the adrenal cortex. Particularly preferred in the method of the invention are pituitary-derived cells.

Consistent with the foregoing paragraph, "cells derived from pituitary" refers [to] the cells or cell lines which are cultured from pituitary tissue derived from animal species, in particular mammalian species, and more particularly, human or murine pituitaries. Illustrated herein is the GH₃ murine cell line ... [Specification, p. 7, line 30- p. 8, line 9].

The results obtained by transforming the rat pituitary cell line GH₃ with expression vectors encoding the β subunits of LH, CG or FSH and the common α subunits are set forth on pp. 14-16 of the specification and in Figure 3.

Although only two of the eight claims on appeal are

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limited to the use of GH₃ cells, these, and the closely-related GH₄ cells, were the only type of regulated secretory granule-containing animal cell considered by the examiner. That is, the prior art relied on by the examiner for the teaching of host cells within the scope of the broad claim, Hellerman and Clayton, are directed to the use of GH₄ and GH₃ cells, respectively. In addition, we direct attention to p. 7, second complete para. of the Answer wherein the examiner states that

the Examiner notes that the rejection under 35 U.S.C. § 103 was drawn specifically to the obviousness of GH₃ and other anterior pituitary cells, and there has been no prosecution to date on the basis of other cell lines which may contain secretory granules- the obvious species (GH₃ cells) also renders the genus (cells having secretory granules) obvious.

Discussion

The examiner has predicated her conclusion of obviousness on the collective teachings of Boime, Hellerman or Clayton, and Vander. Boime describes the construction of expression vectors comprising the DNA sequences encoding the " subunit common to FSH, LH, CG and TSH and/or the \$ subunit of FSH, LH

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or CG. Boime further describes the expression of said DNA sequences in Chinese hamster ovary (CHO) cells in order to obtain heterodimeric hormones. Hellerman describes the expression of a DNA sequence encoding human parathyroid in rat pituitary GH₄ cells using a recombinant expression system. Clayton describes the construction of vectors encoding a fusion sequence comprising the DNA sequence encoding the promoter of the β subunit of the gonadotropin, luteinizing hormone (LH) and the DNA sequence encoding the chloramphenicol acetyltransferase (CAT) receptor. The constructs were used to transform GH₃ cells in order to characterize the activity (analyze the inducibility to forskolin) of the LH- β gene promoter sequence. Vander discloses that, in humans, FSH, LH, ACTH, TSH and growth hormone are produced by anterior pituitary cells. According to the examiner, "[i]t would have been obvious to a person of ordinary skill in the art to produce any one of the reproductive hormones of the claims by using Boime's method, but instead substituting rat pituitary cells as the host cells in view of the disclosures of Hellerman and Clayton that such cells were known in the art to be used as transfection hosts for the expression of

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hormones...." Answer, p. 4. We agree.

As pointed out by the examiner, Boime describes the expression of DNA sequences encoding the claimed human gonadotropins in a mammalian host cell. We acknowledge that rat pituitary GH₃ cells are not the natural source of gonadotropins; however, we find that the teachings of the applied prior art, Hellerman and Clayton, demonstrate that this cell line was known and used by those of ordinary skill in the art as a host cell for the expression of heterologous mammalian DNA sequences, including, *inter alia*, sequences which encode human hormones, at the time the application was filed. Accordingly, we agree with the examiner that the collective teachings of the applied prior art would have suggested the claimed method of producing a human gonadotropin in other known mammalian host cells, such as the rat pituitary cells taught by the applied prior art. *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (the test of obviousness is not the express suggestion of the claimed invention in any or all the references, but rather what the references collectively would have suggested to those

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skilled in the art). Thus, we hold that it would have been ***prima facie*** obvious to one of ordinary skill in the art to produce a human gonadotropin by transforming a regulated secretory granule-containing animal cell with an expression vector capable of expressing a DNA sequence encoding said gonadotropin.

After a ***prima facie*** case of obviousness under 35 U.S.C. § 103 has been established, the burden of going forward shifts to the appellant. ***In re Piasecki***, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). In response, the appellant can submit objective evidence of nonobviousness, such as evidence of unexpected results. ***In re Soni***, 54 F.3d 746, 749, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). In the case before us, the appellant relies on the teachings on pp. 14-16 the specification with respect to the expression of FSH in GH₃ cells and a declaration of Dr. Boime (Paper Nos. 8 and 12), which shows a difference in the glycosylation and sulfation of LH when expressed in GH₃ cells as compared to CHO cells. Declaration, paras. 3 and 4. The appellant argues that (i) the specification data show that FSH is properly processed

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when produced in GH₃ cells, and (ii) the declaration shows that GH₃ cells properly modify the protein [LH] by glycosylation and modify the glycosylation portion by the addition of sulfate, a critical determinant of its bioreactivity *in vivo*." Brief, pp. 7 and 8. According to the appellant these results are surprising because GH₃ cells do not normally produce gonadotropins. Brief, p. 8, last para.

Here, we agree with the appellant that the examiner is merely reiterating her previous arguments and has not given sufficient weight to the showing of unexpected results. Regardless of the strength of the *prima facie* case of obviousness, when an applicant submits objective evidence in rebuttal, the examiner must step back and consider all the evidence anew. *In re Piasecki, supra*. As set forth by the court in *In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976), "An earlier decision should not, as it was here, be considered as set in concrete. * * * Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself." In her response, we find that

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the examiner merely states, without challenging the specification results with respect to FSH, that the appellant's conclusion that GH₃ cells correctly process FSH is unsupported by fact or evidence. Answer, p. 7, last para. She does not challenge the appellant's data set forth in the declaration or the specification, but instead she merely states that the "appellants [sic, appellant's] allegation that 'it is surprising to find that these (GH₃) cells correctly process FSH' remains unsupported by fact or evidence." Answer, p. 7, last para. Thus, we find that the examiner, in effect, is giving no weight to the evidence and is maintaining her original position with her statement that "[i]t remains that GH₃ had been demonstrated to be useful as host cells for recombinant expression of proteins, and that one of ordinary skill in the art would have expected such cells to be useful for the production of FSH for the **reasons of record above.**" [Emphasis added.] **Id.** Absent factual reasons as to the shortcomings of the declaration and specification data, we must assume that the data demonstrate that an unexpected result was obtained for the claimed method of producing the

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human gonadotropins, LH and FSH, in GH₃ cells. Since the issue of the obviousness of the claimed method and cell cultures has only focused on the obviousness of the use of GH₃ as host cells, when faced with the appellant's evidence of unexpected results, at a minimum, the examiner should have allowed the claims specifically directed to this cell line; i.e., claims 3 and 9.

As to the examiner's argument that "the showing that a single possible embodiment, the use of CHO cells as a recombinant host, does not produce a particular result is not sufficient to establish that it is an [sic] the production of that particular result using GH₃ cells is unexpected," it is not clear to us what more she would have the appellant do. The only and, therefore, closest prior art of record shows the recombinant expression of DNA sequences encoding human gonadotropins in CHO cells. There is no burden on the appellant to establish that the claimed method results in an unexpected result with respect to cell lines not raised as an issue in the rejection.

Accordingly, since the examiner has not provided any reasons why the genus of cells having regulated secretory

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granules would have been obvious to those of ordinary skill in
the art at the

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time the application was filed, we reverse the rejection in
its entirety.

The decision of the examiner is reversed.

REVERSED

	William F. Smith)	
	Administrative Patent Judge)	
)	
)	
	Fred E. McKelvey, Senior)	BOARD OF
PATENT)	
	Administrative Patent Judge)	APPEALS AND
)	INTERFERENCES
)	
	Joan Ellis)	
	Administrative Patent Judge)	

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Kate H. Murashige
Morrison & Foerster
2000 Pennsylvania Ave., N.W.
Suite 5500
Washington, DC 20006-1812