

The opinion in support of the decision being entered today was not written for publication and is not precedent of the Board

Paper No. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte JAY W. HEINECKE

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Appeal No. 1999-1273  
Application 08/709,916

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ON BRIEF

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Before Robinson, Spiegel, and Mills, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1, 4 and 6, which are all of the claims pending in this application.

We reverse.

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Claim 1 is illustrative of the claims on appeal and reads as follows:

1. A diagnostic method and screening test for atherosclerosis comprising determining the presence of 3-chlorotyrosine in a test sample of a body tissue at a level which is elevated from about 10-fold to about 100-fold greater than the level in a normal subject.

The prior art references relied upon by the examiner are:

Daughtery et al. (Daughtery), "Myeloperoxidase, a Catalyst for Lipoprotein Oxidation, Is Expressed in Human Atherosclerotic Lesions," Journal of Clinical Investigation, Vol. 94, pp. 437-444 (July 1994).

Domigan et al. (Domigan), "Chlorination of Tyrosyl Residues in Peptides by Myeloperoxidase and Human Neutrophils," The Journal of Biological Chemistry, Vol. 270, No. 28, pp. 16542-548 (July 14, 1995).

#### OPINION

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims, to the applied prior art references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the below-noted rejection, we make reference to the examiner's Answer (Paper No. 12, February 18, 1998) for the examiner's complete reasoning in support of the rejection, and to the appellant's Brief (Paper No. 11, February 2, 1998) for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

### BACKGROUND

Low density lipoprotein (LDL) must be oxidized to trigger the pathological events of atherosclerosis. A mechanism considered for the underlying pathways for oxidation of LDL in vivo involves myeloperoxidase, a heme protein secreted by activated phagocytes. Specification, page 3. Myeloperoxidase uses hydrogen peroxide generated by phagocytes to generate potential microbicidal and cytotoxic agents. Catalytically active myeloperoxidase is present in human atherosclerotic lesions, where it co-localizes with lipid laden macrophages, the cellular hallmark of early atherosclerotic lesions. In vitro studies of inflammation have demonstrated that the myeloperoxidase system oxidizes L-tyrosine to yield 3-chlorotyrosine. Specification, page 4.

The claimed invention relates to a diagnostic method and screening test for atherosclerosis comprising determining the presence of 3-chlorotyrosine in a test sample of a body tissue at a level which is elevated from about 10-fold to about 100-fold greater than the level in a normal subject.

### DECISION ON APPEAL

#### 35 U.S.C. §103

Claims 1, 4 and 6 stand rejected under 35 U.S.C. §103 as unpatentable over Daugherty in view of Domigan.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629, (Fed. Cir. 1996) . Furthermore, the conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

In the present case the examiner relies upon Daugherty as evidence of the presence of myeloperoxidase in human vascular lesions. Daugherty describes that myeloperoxidase may contribute to atherogenesis by catalyzing oxidation reactions in the vascular wall. Answer, page 3. The detection of the myeloperoxidase enzyme in diseased human vascular tissue is found to be strong support for the hypotheses that myeloperoxidase, with its ability to promote lipoprotein oxidation by pathways involving

hypochlorous acid (HOCl) and tyrosyl radical, might be a pivotal element in the development of atherosclerotic lesions. Daugherty, page 442, column 2.

The examiner acknowledges that while Daugherty demonstrates a correlation between the presence of myeloperoxidase enzyme and atherosclerosis, it does not provide a direct correlation of atherosclerosis with 3-chlorotyrosine and does not suggest the detection of 3-chlorotyrosine as a marker for atherosclerosis. Answer, page 4.

The examiner relies upon Domigan for demonstrating that neutrophil hypochlorous acid reacts with tyrosine residues in small peptides and converts them to chlorotyrosine. Chlorotyrosine is indicated in Domigan to be a marker for the production of hypochlorous acid in vivo and for the involvement of myeloperoxidase in inflammatory tissue damage. Answer, page 4; Domigan, abstract. Domigan suggests that it is likely that 3-chlorotyrosine isomer is formed by the activity of myeloperoxidase in human neutrophils because the hydroxyl group on the aromatic ring of tyrosine activates the ortho positions for substitution. Domigan, page 16545.

The examiner concludes that it would have been obvious to one of ordinary skill in the art to determine elevated levels of 3-chlorotyrosine as a screen for atherosclerosis, since Daugherty specifically teaches that myeloperoxidase is found in atherosclerotic lesions and is not present in normal tissue, and that the enzyme promotes lipoprotein oxidation by pathways involving hypochlorous acid and tyrosyl radical, and

Domigan specifically teaches that chlorotyrosine will be a specific marker for the production of hypochlorous acid in vivo, for the involvement of myeloperoxidase in inflammatory tissue damage, and that 3-chlorotyrosine is the likely isomer which is formed. Answer, pages 4-5.

Appellant argues 1) that the examiner's position is not supported by any facts of record or scientific reasoning and thus the examiner has not presented a prima facie case of obviousness, 2) the examiner has engaged in hindsight reconstruction of appellant's invention, and 3) the cited references fail to suggest or identify 3-chlorotyrosine as being a diagnostic for atherosclerosis and do not disclose elevated level of 10 to 100-fold greater of 3-chlorotyrosine than a normal subject. Brief, pages 8-11. For the reasons herein, we agree with the appellant that the examiner has not established a prima facie case of obviousness on the record before us.

At best, the cited references establish that myeloperoxidase is a catalyst for lipoprotein oxidation and is expressed by human atherosclerotic lesions. The cited references also would appear to establish that byproducts of myeloperoxidase are hypochlorous acid and tyrosyl radicals. The examiner has not established with sufficient evidence, and we do not find, that the cited references provide a direct correlation between the presence of elevated levels of 3-chlorotyrosine and the atherosclerotic disease condition.

To supply this omission in the teachings of the applied prior art, the examiner made determinations (Answer, page 5) that direct correlation between the presence of elevated levels of 3-chlorotyrosine and the atherosclerotic disease condition would have been obvious to an artisan. However, this determination has not been supported by any evidence that would have led an artisan to arrive at the claimed invention.

Although the examiner finds that the in vitro investigations of Domigan, using a four amino acid peptide, support the proposition that chlorotyrosine will be a specific marker for the production of hypochlorous acid in vivo and for the involvement of myeloperoxidase in inflammatory tissue damage (Answer, page 6), the examiner points to no evidence showing or suggesting a direct correlation between the presence of elevated levels of 3-chlorotyrosine and the atherosclerotic disease condition, or the relevance of elevated levels of 3-chlorotyrosine of 10 to 100-fold as compared to normal vascular tissue.

In our view, the only suggestion for modifying the cited references in the manner proposed by the examiner to meet the above-noted limitations stems from hindsight knowledge derived from the appellant's own disclosure. The use of such hindsight knowledge of appellant's disclosure to support an obviousness rejection under

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35 U.S.C. § 103 is, of course, impermissible. See, for example, W. L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). It follows that we cannot sustain the examiner's rejections of claims 1, 4 and 6.

CONCLUSION

The rejection of claims 1, 4 and 6 under 35 U.S.C. § 103 is reversed.

REVERSED

Douglas W. Robinson  
Administrative Patent Judge

Carol A. Spiegel  
Administrative Patent Judge

Demetra J. Mills  
Administrative Patent Judge

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