

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

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opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.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. 34

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BOARD OF PATENT APPEALS
AND INTERFERENCES

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JULIAN GORDON, ANDREAS A. KAPSALIS
and RICHARD E. THOMPSON

Appeal No. 94-2247
Application 07/933,971¹

ON BRIEF

Before WILLIAM F. SMITH, METZ and HANLON, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal from the final rejection of claims 1 and 4 through 8, all the pending claims in the application.²

¹ Application for patent filed August 24, 1992. According to applicants, this application is a continuation of Application 07/117,278 filed November 5, 1987, now abandoned

² Similar subject matter was involved in Appeal No. 91-0871 in the parent application. Neither appellants nor the examiner have
(continued...)

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

1. A method for the quantitative determination of the presence of an analyte enzyme in a sample comprising the steps of:

(a) immobilizing the analyte enzyme present in a quantity of sample to be analyzed at a reaction site on a chromatographic medium,

(b) contacting said chromatographic medium with a solution comprising a substrate,

(c) transporting said solution to said reaction site wherein said analyte enzyme catalyzes the reaction of said substrate to produce a detectable reaction product at a rate related to the amount of enzyme present,

(d) transporting said solution and said reaction product from said reaction site to a detection region comprising a length of said chromatographic medium downstream from said reaction site wherein transport continues until said solution reaches the end of said chromatographic medium or until the quantity of solution is exhausted, and wherein the production of said reaction product results in a continuous record of the rate of reaction, and

(e) detecting a signal produced by (i) said substrate, (ii) said reaction product, or (iii) a reactant or product of one or more additional reactions of said reaction product, at a selected site in said detection region.

The references relied upon by the examiner are:

Forgione	3,875,014	Apr. 01, 1975
Deutsch et al. (Deutsch)	4,235,601	Nov. 25, 1980
Kallies	4,298,688	Nov. 03, 1981
Bolguslaski et al. (Bolguslaski)	4,629,688	Dec. 16, 1986

²(...continued)

indicated that the previous decision is relevant to the issues to be decided in this appeal.

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The claims stand rejected as follows:

I. Claims 1 and 4 through 8 stand rejected under 35 U.S.C. § 112, first paragraph, as being nonenabled,

II. Claims 1, 4, 7 and 8 under 35 U.S.C. § 103 as unpatentable over Kallies in view of Forgione and Deutsch, and,

III. Claims 5 and 6 under 35 U.S.C. § 103 as unpatentable over Kallies in view of Forgione and Deutsch, and further in view of Bolguslaski.

We reverse rejections I, II and III.

OPINION

REJECTION I

In regard to issues raised under the enablement requirement of 35 U.S.C. § 112, first paragraph, the examiner argues

The specification is non-enabling for an enzyme catalyzing reaction of a substrate to produce a detectable product at a rate related to an amount of enzyme present as in step (c) of claim 1 and detection of a reaction product resulting in a continuous record of a rate of reaction as in step (d) of the claim. (Examiner's Answer page 3, emphasis in the original)

Since only a portion of the substrate/cofactor solution would be in contact with the immobilized enzyme at any given time, the examiner states the rate of product formation would appear to be more related to the speed of flow of the substrate through the

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chromatographic medium than to the amount of enzyme present. Furthermore, Figures 2a-2d of this application, which illustrate differing amounts of detectable fluorescent reaction products associated with the start up and steady state phases of the analyte enzyme catalyzed reaction, fail to give details of how to determine a rate of reaction from the observed fluorescence.

Appellants state the rate of the enzyme catalyzed reaction can be determined either empirically or derived from the solution flow rate and the concentration of an enzyme substrate or a reaction product at any point along the chromatographic medium downstream from the reaction site, pointing to specification page 7

Transport of the solution containing unreacted members of the substrate/cofactor group and the products of the reaction is such that the concentration of reaction product and/or substrate/cofactor group members present at any point along that length [of the chromatographic medium] is indicative of the rate of reaction at a specific time as determined by the quantity of bound enzyme, the geometry of the enzyme spot and the solution flow rate.

In determining whether a patent specification enables the claimed invention, the Patent and Trademark Office must accept the enabling statements in the specification unless there is reason to doubt their objective truth. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The examiner has not met his burden to provide reasons why the specification does

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not enable one to practice the claimed method. While the examiner has pointed to specific language and examples in the specification, the examiner has not provided any analysis as to why one skilled in the art would not be able to practice any specific step or steps set forth in the claims. For example, why would one not be able to "transport" the solution to the reaction site as required by claim 1 (c)? The language used at this portion of the claim to describe how the enzyme catalyzes the reaction of the substrate appears to only be setting forth what will necessarily occur when the enzyme is placed in contact with the substrate. That the rate of reaction may be dependent on other factors not specified in the claim such as geometry of the reaction site does not mean that the claim is not enabled.

Furthermore, assuming arguendo, that the claims can only be practiced with knowledge of the rate of reaction between the enzyme and substrate, the examiner has not properly established that a person skilled in the art would have any difficulty in either deriving the rate of reaction or determining the reaction rate empirically.

The same analysis applies to the examiner's concern regarding claim 1 (d). The examiner has not established in the first instance that one skilled in the art would have any difficulty in "transporting" the solution and reaction product

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from the reaction site such that the production of the reaction product results in a continuous record of the rate of reaction.

Rejection I is reversed.

REJECTIONS II and III

As developed by the examiner and appellants, the basic issue is whether it would have been obvious to "reverse" the assay of Kallies to obtain the claimed method.

Kallies describes a method for determining an enzyme substrate, i.e. glucose, by dipping a test strip in a liquid sample containing glucose. The test strip comprises a chromatographic filter paper having, in liquid flow order, (1) a first end or "measuring site" for immersing in the sample, (2) a reaction site with immobilized glucose oxidase enzyme, and (3) a detection zone containing an indicator system for measuring a detectable product related to the amount of glucose substrate present in the sample. In operation, the liquid sample is carried by capillary action from the measuring site to the reaction site where the glucose in the sample reacts with the immobilized glucose oxidase to produce a hydrogen peroxide reaction product. Unreacted liquid sample, now containing the hydrogen peroxide reaction product, continues to migrate up the test strip to the detection site where the hydrogen peroxide reacts with peroxidase and an indicator to produce a color which

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provides a determination of the amount of glucose present in the sample.

The examiner's position is that it would have been obvious to use the test strip of Kallies to measure an enzyme analyte instead of a substrate analyte, i.e., to "reverse" which member of the enzyme-substrate reaction is being measured, in view of Forgione's suggestion to measure enzyme analyte with a test device containing enzyme substrate and reaction product indicator.

We do not agree that simply "reversing" the assay of Kallies would have resulted in the claimed assay since a fair "reversal" of Kallies would entail immobilizing the substrate and immersing the test strip in the sample containing the enzyme analyte. The structure of the Forgione device further supports immobilizing substrate reagent, not enzyme analyte as required in the claimed invention, when assaying for enzyme analyte.

The Forgione device comprises a first layer (to which sample is applied) containing substrate superimposed on second layer containing an indicator system. The two layers are attached by an adhesive layer whose main criteria is that only the reaction product of the enzyme-substrate reaction can pass from the substrate layer through into the indicator layer, i.e., the substrate is effectively immobilized from migrating through the rest of the test device.

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Deutsch fails to remedy the deficiencies of Kallies and Forgione. Deutsch, like Kallies, immobilizes the reagent oxidase enzyme when analyzing for the corresponding substrate analyte.

The examiner has not provided reasons why it would have been obvious to immobilize the analyte enzyme on the test strip of Kallies instead of the reagent substrate. Kallies, Forgione and Deutsch all suggest immobilizing the reagent, i.e., substrate, on the test device and applying the sample, i.e., enzyme analyte thereto. The examiner's conclusion that

The test strip and assay procedure of Kallies could have been easily adapted for enzyme assay by supplying the enzyme to the reaction zone of the test strip in a liquid sample and supplying the substrate for the enzyme to the measuring zone as a reagent that reacts with the enzyme as in the assay of Forgione.
(Examiner's Answer page 6, emphasis added)

is not premised upon the correct standard for determining obviousness. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Thus, we agree with appellants that the reasons to reverse the positioning of the known and unknown reactants of Kallies/Forgione/Deutsch in order to arrive at the claimed method are only provided by appellants' disclosure.

We reverse Rejection III for the reasons set forth above. Bolguslaski does not suggest reversing the positioning of the known and unknown reactants of Kallies/Forgione/Deutsch.

Rejections II and III are reversed.

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Administrative Patent Judge Metz, concurring.

I agree with the majority's decision with respect to the rejection under 35 USC 112, first paragraph. However, while I agree with the conclusion of the majority that the examiner has failed to discharge his duty and make out a *prima facie* case of obviousness under 35 USC 103 with respect to the claimed subject matter, I respectfully disagree with the majority's rationale as stated in their opinion above.

Initially, I believe that the starting point for our deliberations should begin with the prior Board decision despite the appellants' and the examiner's decision to ignore it. I disagree with the majority's characterization in footnote [2] of their decision that the claims before the prior panel only involved "similar subject matter" to the claims now before us. In the prior appeal, claim 1 was essentially the same as claim 1 now before us except for the deletion in step (b) that the reaction between the substrate and analyte enzyme to form a reaction product is catalyzed by the analyte enzyme at a rate related to the amount of enzyme present (now recited in step (c) of claim 1). Appellants added a limitation to claim 1, step (d) further defining the "detection region" and added a limitation requiring "wherein the production of said reaction product results in a continuous record of the rate of reaction". This last limitation was apparently added by appellants in response to

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the Board's prior determination that although argued by appellants as a patentable distinction over the prior art, then existing claim 1 did not recite such a limitation. Additionally, I note the rejection considered by the prior panel was founded on the same prior art as the rejection here before us. In the prior appeal, the prior panel affirmed the examiner's rejection but only founded on Kallies and Forgione.

The issue to be decided here has been characterized as "whether it would have been obvious to 'reverse' the assay of Kallies to obtain the claimed method" (page 6 of the majority opinion). I disagree with the statement of the issue. The issue to be decided under 35 USC 103 is whether or not the differences between the subject matter sought to be patented by appellants and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art. Appeals to this Board under 35 USC 134 are from decisions of the examiner, not from the reasons upon which said decisions are based. See McCrady, Patent Office Practice, 4th Edition, Section 234 (1959).

Appellants describe various known prior art techniques for detection of analyte enzymes beginning at page 1, line 22 and concluding at page 5, line 16 of their specification as representative of the level of ordinary skill in this art. Thus, it is apparent from appellants' disclosure and the prior art

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relied on by the examiner that the hypothetical person of ordinary skill in the relevant art is a chemist skilled in quantitative analysis and analytical techniques.

As correctly noted by the majority, Kallies describes a method for determining an unknown (enzyme substrate, glucose) by dipping a chromatographic test strip in a liquid sample containing glucose but in an unknown amount. The test strip, like appellants' test strip, has, in liquid flow order, (1) a measuring site for immersion in the sample containing the unknown, (2) a reaction site with immobilized enzyme (glucose oxidase) thereon, and (3) a detection zone including an indicator for quantifying detectable product related to the amount of enzyme substrate (glucose) present in the sample. In operation, as in appellants' method, the sample is "transported" by capillary action from the measuring site to the reaction site where a reaction product is formed. The unreacted sample and reaction product are transported via capillary action, as in appellants' method, to a detection site where the reaction product reacts with an indicator which produces color. The color produced provides a determination of the amount of glucose present in the sample. The procedure described by Kallies is said to permit "at least semiquantitative detection of glucose." (column 4, lines 39 through 41).

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Appellants' claim 1 reads on the quantitative determination of glucose oxidase by immobilizing an unknown amount of glucose oxidase on the chromatographic medium at a reaction site, contacting the chromatographic medium with a solution of glucose of known concentration, transporting the glucose to the reaction site wherein said glucose oxidase catalyzes the reaction of said glucose to produce a detectable reaction product at a rate related to the amount of glucose oxidase present, transporting said glucose and said reaction product to a detection region downstream from said reaction site, and detecting a signal produced by said glucose or said detectable reaction product. Thus, the salient differences from the method claimed by appellants and the method disclosed by Kallies are: in appellants' method the amount of enzyme (glucose oxidase) is unknown rather than the amount of substrate (glucose); and, the production of the reaction product in appellants' method is claimed to result "in a continuous record of the rate of reaction".

From Kallies' disclosure, the person of ordinary skill in the art would have understood that appellants' "substrate" would have been expected to "travel" by capillary action up the chromatographic strip to a "reaction site" where an enzyme was immobilized and that the enzyme and the substrate would have been expected react to form a detectable reaction product. The

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skilled routinier would also have understood and expected from Kallies' disclosure that the reaction product would also "travel" by capillary action to the detection zone on the chromatographic strip where the reaction product would have been expected to produce a detectable signal. In re Sovish, 769 F.2d 738, 226 USPQ 771 (Fed. Cir. 1985); In re Preda, 401 F.2d 825, 159 USPQ 342 (CCPA 1968); In re Jacoby, 309 F.2d 513, 135 USPQ 317 (CCPA 1962). Indeed, since appellants' "analyte enzyme" and "substrate" read on the glucose and glucose oxidase taught by Kallies, the same chemistry is necessarily involved in appellants' method of claim 1 as is involved in Kallies'.

In my view, and recognizing that the representation which follows is an over-simplification of the involved chemical reaction before us, given a known reaction of $A(\text{reactant}) + B(\text{reactant}) = C(\text{product},)$, and given known concentrations of either reactant and product, it would have been obvious to the person of ordinary skill in the art to quantitate for the unknown in the above reaction whether the unknown is called "analyte enzyme" or "substrate". Stated another way, in the above example, if you begin with the knowledge of how much A is present and can react A with unknown amount of B to obtain a known amount of C, then the amount of B can be readily determined. Thus, I agree with the conclusion implicit in the examiner's statement of the rejection that, at the time appellants' invention was made,

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it would have been obvious to assay for an analyte enzyme rather than a substrate using Kallies' method and test strip.

Nevertheless, the question to be resolved under the statute is whether or not it would have been obvious to perform the assay in the manner claimed by appellants. In re Geerdes, 491 F.2d 1260, 180 USPQ 789 (CCPA 1974).

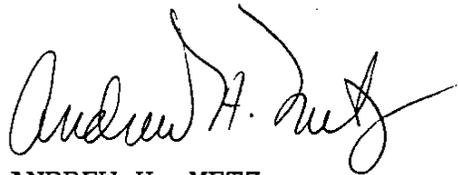
Appellants urge that by immobilizing the quantitatively unknown reactant (analyte enzyme) on the chromatographic medium rather than the quantitatively known reactant (glucose oxidase) as in Kallies, appellants' method of quantitative determination for the presence of an analyte enzyme is also "capable of determining and maintaining a record of the instantaneous rate of reaction at any given time including the steady state rate of reaction after the start up period" (page 2 of appellants' brief, emphasis in the brief). Appellants argue that the examiner has failed to establish that this claimed feature would have been *prima facie* obvious from the applied prior art. However, this feature is not recited in claim 1, step (d). What is recited in claim 1, step (d) is that the production of the reaction product "results in a continuous record of the rate of reaction". Therefore, the examiner's burden to establish a *prima facie* case of obviousness included establishing that this feature, part of appellants' claimed invention, would have been obvious to a

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person of ordinary skill in the art at the time appellants' invention was made. This the examiner has failed to do.

The examiner has failed to explain how Kallies or any other reference relied on by the examiner describes the creation of a continuous record of the rate of reaction for the described and tested for reactants. Indeed, the only reference in the Examiner's Answer to this claim limitation is found at page 11 in the examiner's discussion of the rejection under 35 USC 112. Accordingly, the examiner has not made out a *prima facie* case of obviousness with respect to the claimed subject matter.

Finally, I note that performing the recited steps of (a) through (e) in claim 1 will not quantitate the amount of analyte enzyme in the sample. In order to quantitate the amount of analyte enzyme present, the claimed method would require a step of comparing the detected signal from step (e) with a standard signal obtained from known concentrations of analyte enzyme. However, this problem could be easily resolved by adding such a step to the claimed method by way of amendment.



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