

MAY-26-95 FRI 18:48

P.02

Original Specification (#1)

WO 94/13830

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PCT/DE93/01085

Device for Performing Urease Tests on Combined Antrum/Corpus Biopsies to
Diagnose Gastrointestinal Illnesses

~~Translator's note: Throughout the document the term 'carrier plate' is used to maintain~~
5 consistency with the English abstract of the patent. A better term would perhaps be
~~'locator plate'.~~

The invention concerns a device for conducting combined urease tests on antrum/corpus
biopsies for diagnosis of gastrointestinal disorders.

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Gastrointestinal disorders such as duodenal or gastric ulcers, and especially chronic,
active gastritis, are closely associated with the partial or diffuse colonization of
Helicobacter pylori (HP) in the stomach. HP, also known as *Campylobacter pylori*, is a
bacterium which catabolizes urea. The general indicator of bacteria such as HP which
15 catabolize urea was described by Stuart et al. (*J. Bacteriol.* 1945, 49, 437) and
Christensen (*J. Bacteriol.* 1946, 52, 461). Regarding the above-mentioned illnesses, HP
is regarded as an established cause of chronic Type B gastritis (Rauws et al.,
Gastroenterology 1988, 94, 33). In the case of an ulcer, HP represents a risk factor for
predisposition of duodenal ulcer recurrence (Coghlan et al., *Lancet II*, 1987, 1109). In
20 recent years, therefore, more and more reliable and, above all else, more practical
indicator methods for HP have been sought. For reasons of ease of implementation and
reduced cost-outlays, the analyses of biopsy probes with urease tests have acquired
increased significance as opposed to very sensitive and specific culture techniques.

25 A culture medium for differentiation of microorganisms which catabolize urea was
described by Christensen (*J. Bacteriol.* 1946, 52, 461) and based on the breakdown of
urea by microorganisms that contain urease. The decomposition of urea into carbon
dioxide and ammonia leads to an alkaline reaction in the medium, which is signalled
when the color-indicator, phenol red, turns from yellow to red.

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WO 94/13830

3

PCT/DE93/01085

A modified quick-test which offers diagnostic advantages when the specimen exhibits only a limited colonization of *Helicobacter pylori* was described by Malfertheiner (*Acta Therapeutica*, 1988, 14, 205).

- 5 According to Börsch et al. (*Immun. Infekt.* 1989, 17, 83-90) the combined examination of antrum and corpus biopsies generally affords a superior diagnostic sensitivity and specificity for indication of the HP colonization of the stomach when compared with a single biopsy. Additionally, the results are thoroughly comparable to that of the more sensitive culture techniques. The combination of two antral urease tests is definitely
- 10 inferior to the combined examination through biopsies of the antrum and corpus. According to Börsch et al, the combined urease tests of an antrum/corpus biopsy represent efficient diagnostic procedure with regard to expense and results. Urease tests are particularly the method of choice when the more sensitive, and generally more costly, culture techniques are not available.

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- In EP-PS 204-438 a procedure for determining the presence of urease in stomach material was described. This procedure used a combination of urea, a bactericide which sharply hindered the growth of the urease-producing organism, and a pH-indicator, (for example, phenol red) in a chemical medium, essentially bacteriological agar. The device which
- 20 EP 204 438 illustrated in Figures 1 through 3 consists of a rectangular plate in which a small bowl fitted with a flexible covering can be used to receive the agar described above. This device is commercially available as CLO-Test®.

- The devices which have been previously described, and which are generally used for
- 25 urease tests, essentially consist of simple, closeable containers which serve to receive either a corpus or an antrum biopsy. These containers must be correspondingly marked or tediously labeled so that the biopsies are not confused. Because these containers (for example, Eppendorf tubes) are very small, it is not possible to label them with the important patient data, with clinical documentation, and/or with test times and results.
- 30 Through use of appropriate labels, a careful marking with the important patient data is usually avoided for economic reasons. In routine laboratory operation, then, it can

MAY-26-95 FRI 18:49

P.04

WO 94/13830

4

PCT/DE93/01085

happen that biopsies which were taken could be falsely classified or biopsies of several patients could be confused.

Devices which do not have these disadvantages and which allow the simultaneous
5 reception of the antrum and corpus biopsies for the combined urease test of antrum/corpus biopsies have, up until now, not been available because of the current state of technology.

The task of this invention, therefore, is to provide a device which allows the performance
10 of combined antrum/ corpus tests for diagnosis of gastrointestinal disorders and which provides for those using the device a distinctive classification of the biopsies taken of the antrum and corpus. The goal of this invention is, particularly, to offer the examining physician a simple, quick, and sure operation of the device, and to prevent the confusion of the biopsies of several patients.

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A device has been invented which fulfills this task according to Claim #1. It is equipped with:

- a) a carrier plate,
- 20 b) a schematic representation of the stomach on the carrier plate,
- c) at least one opening in the aforementioned carrier plate which corresponds to the corpus and antrum, respectively, in the schematic representation,
- 25 d) an evaluation scale for assessment of the urease tests, and
- e) an area for patient data and clinical documentation.

In a model of the invention, the openings described above serve to receive and to fix in
30 place commonly used, closeable specimen containers which hold the medium used for the

MAY-28-95 FRI 18:50

P. 05

WO 94/13830

5

PCT/DE93/01085

urease test. The schematic representation of the stomach is either pressed or engraved onto the carrier plate of this model.

A particularly preferred device is one in which the openings described above are openings of containers which are permanently connected to the carrier plate, these containers holding a culture medium for the urease test being performed and having a sealable lid. A cover which is secured to the carrier plate is the preferred sealing device. An adhesive seal in the form of transparent foil, for example, can serve as an alternate. If such an adhesive seal is used, it can be imprinted with the schematic representation of the stomach. In this way the schematic representation is applied to the carrier plate not through printing or engraving, but with the printed foil. The openings in the carrier plate can be sealed either with separate pieces of foil or by a single foil piece. It is preferable to use only a single foil to seal the openings. Most preferable is for the schematic representation of the stomach to be printed or engraved directly on the carrier plate and the openings sealed with a cover or with transparent, unprinted foil. In this way, proper classification of the antrum and/or corpus biopsies is guaranteed even if the adhesive seal is completely removed.

In a later model the carrier plate contains more than one opening in the areas corresponding to the corpus and to the antrum. This offers the advantage of allowing several simultaneous antrum/corpus biopsies for the combined antrum/corpus urease test. With the additional comparison biopsies allowed through use of this same carrier plate, the risk of false-positives on the urease tests is significantly reduced.

The device which was invented can be used in combination with the urease tests which are commonly used. A gel-like substrata is generally used containing per 1,000g: .1g yeast extract, .1g potassium dihydrogen phosphate, .6g phenol red, 14.4g agar, .1g dextrose, 19.2g urea, 2.9 ml vitamin solution, and .1ml solution of trace elements.

The vitamin solution referred to is prepared by dissolving .198 g D (+) vitamin H, 1.977 g niacin, .988g vitamin B₁₂, .988g para aminobenzoic acid, .494g deuterium

MAY-26-95 FRI 18:50

P.06

WO 94/13830

6

PCT/DE93/01085

pantothenic acid-sodium salt, 4.942 g Pyridoxamine dihydrochloride, and 1.977g vitamin B₁₂ in 988.435g of distilled water with sterile filtration following. The solution of trace elements referred to is prepared by dissolving .049g of barium chloride · 2 H₂O, .198g neutral potassium iodide, .198g potassium bromide, .099g boric acid, .049g tin chloride, .049g lithium chloride, .198g zinc chloride · 2 H₂O, .099g copper (II) sulfate · 5 H₂O, .198g cobalt chloride · 6 H₂O, .99g manganese dichloride · 4 H₂O, 7.919g Titriplex® III · 2 H₂O, .01g iron (II) sulfate · 7 H₂O, and .099 sodium molybdate · H₂O in 989.844g distilled water with sterile filtration following. Pure substances and/or substances for the performance of the analysis (yearly) are chiefly used.

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The basic preparation, containing no urea, is autoclaved and mixed with the thermolabile components at a temperature of less than 62°C to produce the ready-to-use preparation. The pH factor of the substrate is adjusted to 6.0 ± .1.

15 The device we have invented provides an easily operated aid to establishing a diagnosis of gastrointestinal illnesses by allowing the sensitive and specialized combination urease tests for antrum/corpus biopsies to be performed. The schematic representation of the stomach on the carrier plate with containers in the areas of the corpus and antrum, as schematically represented, ensures a simple classification of the sample and thereby

20 reduces the possible confusion of the biopsies taken from the antrum and corpus. The device is easily operated in all cases and, because the patient data relating not only to the antrum, but also to the corpus, as well as clinical data such as test time and results, is found on a single carrier near the biopsy, possible confusion or exchanges are avoided. The evaluation scale found on the carrier plate allows for a rapid and clear determination

25 of diagnosis through a direct comparison of color changes which occur in the side-by-side culture media containing the antrum and corpus biopsies. The biopsies remain together on the carrier plate and can also be compared after 24 hrs. to any color changes in the urease tests.

30 The form of the device permits an advantageous storing of the specimens.

MAY-26-95 FRI 18:51

P.07

WO 94/13830

7

PCT/DE93/01085

The invention is described in the following through use of examples:

Example 1:

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Fig. 1 shows a device for performing combined urease tests on antrum and corpus biopsies for diagnosis of gastrointestinal illnesses. A schematic representation of the stomach (2) is found on the carrier plate (1). On each of the places corresponding to the antrum and to the corpus, an opening (3) is located. An evaluation scale (4) for assessment of the test results, preferably with colored markings, is located on the carrier plate (1). The field (5) which is found on the carrier plate collects patient data and clinical documentation. That is, the final assessment of the combined urease tests of an antrum/corpus biopsy can be entered here. The field (6) contains further information on the combined urease test, such as manufacturer or general comments.

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Example 2:

Fig. 2 shows a cross-section of a device corresponding to Fig. 1 for the performance of combined urease tests on antrum/corpus biopsies for diagnosis of gastrointestinal illnesses. During these tests the carrier plate (1) in the device portrayed in Fig. 1 has a container (4) which is filled with substratum (2). This container (4) is sealed with the help of a foil (3). The location of the container (2) in Fig. 2 is identical to the opening (3) in Fig. 1.

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Example 3:

The device represented in Fig. 1 serves to receive the scalable containers or tubes which contain the substratum used for the urease tests.

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MAY-26-95 FRI 18:52

P.08

WO 94/13830

3

PCT/DE93/01085

Fig. 3 shows a cross-section of a device for the performance of combined urease tests on antrum/corpus biopsies for diagnosis of gastrointestinal illnesses, during which the tubes mentioned are placed in the openings (2) in the carrier plate (1). The tubes are then fixed
5 in place with the help of rubber washers and/or rings installed in the openings. The position of the openings (2) in Fig. 4 corresponds to the position of the openings (3) in Fig. 1 and provides for a clear alignment to either corpus or antrum.

Example 4:

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Fig. 4 shows a cross-section of a device which combines the features found in the alternatives discussed in Examples 2 and 3. The container (4) which fits into the carrier plate (1) in Fig. 2 is provided with a rim that protrudes above the level of the carrier plate (1) which virtually leads to the tubes (2) that are integrated into the carrier plate in Fig. 4.
15 The rim of the container (2) that stands above the plane of the carrier plate (1) allows a sealing device, for example, a cover in the form of a sealing stopper (4) (Fig. 4), to be attached. Another preferred closure is a screw-on cap with cylindrical in-lays which forces inner contact of the biopsy with the substratum used for the urease test by pushing the biopsy down into the substratum. The substratum (3) used in the urease test can be
20 put into this container (2). The container (2) (Fig. 4) lies in the region of the openings (3) represented in Fig. 1 and allows for classification of corpus and antrum.

Example 5:

25 Fig. 5 shows an overview of a particularly preferable model of Fig. 1 and/or of the device described in the previous examples. The numbering corresponds to Fig. 1.

MAY-26-95 FRI 18:52

P.09



WO 94/13830

9

PCT/DE93/01085

Claims

1. The device described is for the performance of urease tests on combined
5 antrum/corpus biopsies for diagnosis of gastrointestinal illnesses, ~~This device~~ ^{comprising}
~~possesses~~
a) a carrier plate,
b) a schematic representation of the stomach on the carrier plate,
10 c) at least one opening in the carrier plate in the locations corresponding to the
corpus and to the antrum on the schematic representation,
d) an evaluation scale for assessment of the urease tests, and
15 e) a field for patient data and clinical documentation.
2. The device described in Claim 1 is characterized by the fact that the openings
20 mentioned are openings for containers which are permanently connected with the
described carrier plate, and that the containers hold the substrate for the urease tests,
and that each container has a cover.
3. The device described in Claim #2 is characterized by the fact that the cover has an
adhesive seal.
- 25 4. The device described in Claims #1-3 is characterized by the fact that the schematic
representation of the stomach is on the adhesive seal.

MAY-26-95 FRI 19:18



P. 05

WO 94/13830

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PCT/DE93/01085

5. The device described in Claim #2 is characterized by the fact that the container has a rim that stands higher than the plane of the carrier plate.
6. The device described in Claim #2 or 5 is characterized by the fact that the cover is provided with a screw-type closure that has a cylindrical insert which presses the biopsy referred to into the substratum.
7. The device described in Claim 1 is characterized by the fact that the openings for reception and fixation of the sample receptacles serve to hold the substratum used in the previously mentioned urease test.
8. The device described in Claim #2, 5, or 7 is characterized by the fact that the schematic representation of the stomach referred to is pressed or engraved into the carrier plate.
9. The device described in the above Claims is characterized by the fact that for the urease test a gel-type substratum with a pH value of between 5.9 and 6.1 is used. Per 1,000 g the substratum contains: 0.1g yeast extract, 0.1g potassium dihydrogen phosphate, 0.6g phenol red, 14.4g agar, 0.1g dextrose, 19.2g carbamide, 2.9 ml vitamin solution, and 0.1 ml trace elements.
10. The device described in Claim #9 is characterized by the fact that the vitamin solution referred to is manufactured by dissolving .198g D (+) vitamin H, 1.977g niacin, .988g vitamin B₁, .988g para aminobenzyne carboxylic acid, .494 g denterium pantothenic acid-sodium salt, 4.942g Pyridoxamine dihydrochloride, and 1.977g vitamin B₁₂ in 988.435g of distilled water with sterile filtration following. The solution of trace elements referred to is prepared by dissolving .049g of barium chloride · 2 H₂O, .198g neutral potassium iodide, .198g potassium bromide, .099g boric acid, .049g tin chloride, .049g lithium chloride, .198g zinc chloride · 2 H₂O, .099g copper (II) sulfate · 5 H₂O, .198g cobalt chloride · 6 H₂O, .99g manganese

MAY-26-95 FRI 19:18



P.04

WO 94/13830

11

PCT/DE93/01085

dichloride · 4 H₂O, 7.919g Titrplex® III · 2 H₂O, .01g iron (II) sulfate · 7 H₂O, and
.099g sodium molybdate · H₂O in 989.844g distilled water.

Figure 5:

- 5 A = Patient
B = Date
C = Time
D = Results
E = Findings
10 F = positive
G = negative

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