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(54) Title: METHOD OF COLLECTING A GASTROINTESTINAL TRACT SAMPLE

(57) Abstract: A method for collecting a sample from a patient, particularly for detection of colorectal cancer or other gastrointestinal pathological conditions or diseases, comprises collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient.

# "Method of Collecting a Gastrointestinal Tract Sample"

## FIELD OF THE INVENTION

This invention relates to a method for collecting a sample from a patient for subsequent use in a detection of an analyte in the sample. In one particular embodiment, this invention relates to a method for collecting a sample from the lower gastrointestinal tract of a patient for the purposes of subsequent detection in the sample of occult blood or one or more other indicators of a pathological condition such as colorectal cancer.

## BACKGROUND OF THE INVENTION

Colorectal cancer (CRC) is reported to be the second leading cause of cancer death in the United States. The cumulative lifetime risk of developing CRC is 5 to 6 percent and it equally affects both men and women. Screening for CRC has been recommended by the American Cancer Society since 1980 and other organizations, such as the American College of Physicians and the United States Preventative Services Task Force, have more recently supported screening of average risk patients (i.e. patients without a family history or prior personal history of colon cancer or adenomatous polyps). Despite these recommendations widespread implementation of CRC screening has not yet occurred.

The detection of occult gastrointestinal bleeding is a common method for screening for colorectal cancer. A well known and widely-used clinical reagent for the detection of occult blood in a sample, particularly a faecal sample, is guaiac (also known as gum guaiac or resin guaiac). The faecal occult blood test (FOBT) most commonly used in clinical practice is Hemoccult II (SmithKline Diagnostics, San Jose, California, USA), which is a guaiac-based test that detects occult blood in a faecal sample on the basis of the pseudoperoxidase activity of heme or haemoglobin. Hydrogen peroxide in the developing reagent converts colourless guaiac to a blue colour in the presence of pseudoperoxidase activity. Other chromogens which may be used instead of guaiac in these tests include orhodianiside and tetramethylbenzidine. It should be noted that a positive FOBT is not specific for cancer or blood as other causes of gastrointestinal bleeding (i.e. gastritis, peptic ulcer disease, etc.) and other substances (red meat, raw vegetables, etc.) can cause a false positive result.

Prior Australian Patent No. 665956 (International Patent Application No. PCT/US92/04425) notes that among the many analytical systems used for detection and/or determination of analytes, particularly analytes of biological interest, are chromatographic assay systems. Among the analytes of biological interest frequently assayed with such chromatographic assay systems are proteins, such as haemoglobin, assayed in determinations of faecal occult blood as an early indicator of gastrointestinal disorders such as colorectal cancer. Such chromatographic assay systems are frequently used by physicians and medical technicians for rapid in-office diagnosis and therapeutic monitoring of a variety of conditions and disorders. They are also increasingly used by patients themselves for at-home monitoring of such conditions and disorders.

Among the most important of such chromatographic systems are the "thin layer" membrane-based systems in which a solvent moves as a solvent front across a thin, flat absorbent medium (e.g., nitrocellulose membrane). Among the most important of the assays that can be performed with such thin layer systems are immunoassays, which depend on the specific interaction between an antigen or hapten and a corresponding antibody. The use of immunoassays as a means of testing for the presence and/or amount of clinically important molecules has been known for some time.

Chromatographic techniques used in conjunction with immunoassays include a procedure known as immunochromatography. In general, this technique uses a disclosing reagent or particle that has been linked to an antibody which is specific to the analyte to be assayed, forming a conjugate. This conjugate is then mixed with a specimen and, if the analyte to be assayed is present in the specimen, the disclosing reagent-linked antibodies bind to the analyte to be assayed, thereby giving an indication that the analyte to be assayed is present. The disclosing reagent or particle can be identifiable by colour, magnetic or fluorescent properties, radioactivity, specific reactivity with another molecule, or another physical or chemical property. The specific reactions that are employed vary with the nature of the analyte being assayed and the sample to be tested.

The present invention is particularly, but not exclusively, directed to collection of samples from the lower gastrointestinal (GI) tract of a patient for occult blood detection, for example in screening for colorectal cancer. As previously described, guaiac- or other chromogen-based testing provides a colorimetric assay system for detection of haemoglobin in a sample, however because of the large

number of false positives obtained in guaiac testing, the use of two or three guaiac tests has been recommended in screening programs , confirmed when positive by an immunological test for human haemoglobin (Favennic L., Kapel N., Meillet D., Chochillon C. and Gobert J.G., *Annales de Biologie Clinique*, **50**(5):311-3, 1992). More recently, a combination of guaiac and immunological testing has been suggested (Allison, J.E., Tekawa, I.S., Ransom, L.J. and Adrian, L.L. *N. Engl. J. Med.*, **334**:155-9, 1996).

It is an object of the present invention to provide a method for collecting a sample from the lower GI tract of a patient which is simple and economic, and which enables subsequent detection and/or determination of analyte in the sample to be readily carried out, for example using a guaiac- or other chromogen-based test, and/or an immunochromatographic or other immunodiagnostic procedure.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a method for collecting a sample from a patient, which comprises collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient.

As used herein, references to collecting a sample directly from the lumen of the lower gastrointestinal tract of a patient are to be understood as referring to intra-rectal collection of the sample from the patient, for example, by a lower rectal lavage or wash procedure or by use of a swab, brush or similar collecting device introduced into the lower rectum of the patient, as described below.

In another aspect, the present invention provides a method for detecting a pathological condition or disease in the gastrointestinal tract of a patient, which comprises the steps of:

(i) collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient; and

(ii) detecting the presence in the sample, if any, of an analyte indicative of the pathological condition or disease.

The pathological condition may be, for example, colorectal cancer, and the analyte detected in the sample is occult blood (which may be detected by guaiac- or other chromogen-based tests and/or immunochromatographic assays for haemoglobin). Unless the patient has been previously subjected to the dietary restrictions which are usually applied in order to reduce false positive results when the guaiac-based test is used, an immuno- chromatographic test for haemoglobin is preferred. Nevertheless, a guaiac-based component to the test may assist in protecting against a false negative result in an immunoassay due to a prozone effect arising from sampling a high concentration of blood (see, for example, International Patent Application No. PCT/AU99/014014 – Publication No. WO 00/29852 – the contents of which are incorporated herein by reference).

Accordingly, in a further aspect the present invention provides a method for detection of occult blood as indicative of a pathological condition or disease in the gastrointestinal tract of a patient, which comprises the steps of:

(i) collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient; and

(ii) detecting the presence of blood, if any, in the sample indicative of the pathological condition or disease by (a) a guaiac- or other chromogen-based test for haemoglobin, or (b) an immunochromatographic assay for haemoglobin, or (c) a combination of (a) and (b).

Alternatively, or additionally, the collected sample may comprise cells and/or cell debris which may be subjected to cytological examination, and/or free proteins, nucleic acids and their degradation products, all of which may be useful for analysis for indications of colorectal cancer or other gastrointestinal pathologies or diseases.

In the method of the present invention, the sample is collected directly from the lumen of the patient's lower gastrointestinal tract, preferably by a lavage or wash procedure as described below. Alternatively, however, the sample may be a directly representative sample of the contents of the lower gastrointestinal tract which can be expected to include any residual occult blood or other

indicators of a pathological condition or disease transported into the lower region of the gastrointestinal tract by stool passage from higher up the gastrointestinal tract.

In the most preferred embodiment of this invention, the sample is collected by a lower rectal lavage or wash procedure in which a suitable wash fluid is introduced into the lower rectum to wash the inner wall of the gastrointestinal tract, and the wash fluid is subsequently aspirated and collected as the sample for subsequent testing.

Suitable wash fluids include both water and saline. The wash fluid may also contain compatible surfactants, buffers, and similar additives.

In an alternative embodiment of this invention, the sample may be collected directly using a fibre-tipped swab, or a brush or similar collecting device having flexible or semi-flexible bristles which is inserted into the lower rectum to obtain a direct sample.

The swab, brush or other collecting device is then added to a fluid in a test tube or similar reagent container to transfer the sample into the fluid for subsequent testing. This fluid may also be used to lubricate the swab, brush or other collecting device prior to collection of the sample. Preferably, the fluid contains a compatible surfactant both to act as a lubricant for the collecting device and to assist in the extraction and dispersion of the collected sample for subsequent testing.

Throughout this specification, unless the context requires otherwise, the word "comprise", and or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia or elsewhere.

DETAILED DESCRIPTION OF THE INVENTION

Whilst the present invention is particularly useful in faecal occult blood testing as described in detail herein, it is to be understood that the method as broadly described herein may be used to obtain a sample from the lower GI tract for subsequent testing to detect the presence of one or more other indicators of a pathological condition, for example, tumour-derived antigens, in addition to or instead of faecal occult blood testing. Thus, the method of this invention may also be used to recover cellular debris, DNA, RNA or the like in the sample for subsequent analysis, for example, for molecular markers of cancer and other pathological conditions, or for the presence of pathogens.

A variety of formats for the faecal occult blood (FOB) test are known in the art (see, for example, US Patent Nos. 3996006; 4225557; 4789629; 5064766; 5100619; 5106582; 5171528; 5171529; and 5182191). The majority of test formats are based on the chemical detection of the heme groups present in faecal material as a breakdown product of blood. In such tests, the pseudoperoxidase nature of the heme group is used to catalyse a colorimetric reaction between an indicator dye and peroxide. The oxygen sensitive dye can be gum guaiac, orthodianisidine, tetramethylbenzidine, or the like, with guaiac being preferred.

Most existing faecal occult blood tests (FOBTs) use a sampling stick or paddle to take smears directly from the surface of a collected faecal sample. European Patent Application No. EP 0 727653 discloses the use of a brush device having stiff bristles to collect a sample from the surface of faecal material directly on the bristles. Many colorectal cancers or their precursors (e.g. adenomas > 1cm), bleed into the lumen of the small intestine. As these malignancies arise as protrusions from the wall of the intestine they make contact with the surface of the stool in their region of contact as the stool passes that point. The blood, therefore, may not be evenly distributed through or over the stool. As a result, existing tests that rely on surface sampling of the stool may or may not sample from that portion of the stool where blood is present.

International Patent Application No. PCT/AU99/00310 (WO 99/56103) discloses the use of a brush or brush-like device having flexible or semi-flexible bristles as a device for obtaining a sample derived from faecal material, and particularly stool, in fluid such as water, particularly for the detection of occult blood as an indicator of colorectal cancer (CRC) or its precursor conditions.

If the stool or other faecal material is sampled in a fluid, for example, when it is in the water of the toilet bowl, there is a better opportunity to gain a representative sampling of the whole stool. This is particularly the case where a small brush (e.g. a small artist's paint brush having bristles about 1 to 2 cm in length) is used for sampling. A brush may be used to "paint" the surface of the stool so as to displace any blood on the surface of the stool into the water surrounding the stool. The flexible or semi-flexible bristles of the brush will be relatively "open" during this brushing and sampling process, but will "close" as the brush is withdrawn from the water, thereby keeping a sample of the water (and any blood contained therein), surrounding the stool within the interstitial spaces of the bristles. This sample may then be transferred to a suitable assay device for subsequent testing.

As previously described, colorectal cancers and adenomas often bleed into the lumen of the large bowel. Initially, only a small, localised amount of blood leakage may occur, leading to isolated spots or areas of blood occurring on the surface of faecal material in the large bowel which will be exposed to the blood first. Similarly, almost all colorectal cancers and all adenomas occupy only a small portion of the diameter of the large bowel. Therefore, it is also likely that the blood from such lesions will be striped along the faecal material.

Collection of a sample from the surface of faecal material as described above has the disadvantage that it relies on patient compliance in obtaining appropriate samples for FOBT testing. Furthermore, since it relies on detecting occult blood on the surface of the faecal material, and any blood present may not be evenly distributed over the surface, there is a real possibility that a surface sample may not sample from that area of the surface where blood is present, leading to a false negative test result.

The direct sampling of the lower gastrointestinal tract of the patient in accordance with the method of the present invention addresses these disadvantages of previous collection methods. Firstly, patient compliance is not relied on in sampling as the sample is taken intra-rectally from the patient by a doctor, nurse or other health professional. Secondly, the sample is taken directly from the lower gastrointestinal tract of the patient and, particularly when the preferred lower rectal lavage or washing method is used, this ensures that the fact that blood may only be present in isolated areas or spots does not prevent the collection of a more representative sample than that obtained by sampling faecal material.

Direct rectal examination (DRE) has been proposed as a method of obtaining a faecal sample for CRC screening, as DRE is commonly performed as a routine procedure in prostate cancer screening. However, studies have shown that only a small percentage of colorectal cancers are within reach of such examination and it does not provide a reliable method of obtaining a sample where blood may only be present in isolated areas or spots (Winawer, S.J., *et al.*, "Colorectal cancer screening: clinical guidelines and rationale", *Gastroenterology* **112**:594-642, 1997). Use of a swab or a brush or similar sampling device or of the preferred lower rectal lavage or washing method in accordance with the present invention provides significantly better reach and sampling capability than that provided by DRE. It should be understood, however, that the direct sampling of the lower gastrointestinal tract in accordance with the present invention may be performed at the same time as DRE of the patient, for example by use of a modified medical examination glove or fingerstall which is specially adapted to directly sample the lower GI tract in accordance with the present invention either by direct collection of a sample from the inner wall of the lower GI tract using a swab, brush or similar collecting device or by the lower rectal lavage or wash procedure as described above.

The detection of an analyte in the sample may be performed using a guaiac or other chromogen-based test for the detection of occult blood in the sample. Alternatively, or additionally, the detection of an analyte in a sample may be detection of occult blood (or other diagnostic antigens) in the sample by means of a chromatographic procedure, particularly by an immunochromatographic or other immunodiagnostic procedure which is well known in the art. Suitable immunochromatographic procedures are described, by way of example, in US Patent Nos. 5591645 and 5622871, the disclosures of which are incorporated herein by reference.

Preferably, detection of an analyte such as occult blood in the sample is carried out using a testing device and methods as disclosed in International Patent Application No. PCT/AU98/00830 (WO 99/18436), the contents of which are incorporated herein by reference. Embodiments of the testing device disclosed in this International patent application are specifically disclosed for FOB testing, including guaiac testing, immunochromatographic testing, or a combination of both types of testing in a single testing device.

The direct method of collection of samples from the lower gastrointestinal tract in accordance with the present invention also enables collection of cells and cell debris, as well as free proteins, nucleic acids and their degradation products, all of which may be useful for analysis for indications of colorectal cancer or other pathologies. In particular, cells and cell debris may be used for cytological examination in a manner similar to the use of Pap smears for identification of cervical cancer cells. While aberrant cells are frequently identified by microscopic examination by eye, significant progress continues to be made with computer assisted cytological image analysis. These technologies offer the potential for automated screening of large numbers of samples, without the risk of human error caused by fatigue, inattention, etc. The detection of aberrant cells may be further assisted if a stain or other identifier is used that specifically reacts with a cell-associated marker of pathology (protein/DNA/RNA, etc).

Further features of the present invention are more fully described in the following Example(s). It is to be understood, however, that this detailed description is included solely for the purposes of exemplifying the present invention, and should not be understood in any way as a restriction on the broad description of the invention as set out above.

## EXAMPLE

A sample is obtained intra-rectally from the lower GI tract of a patient by the following procedure:

An aliquot (5 ml) of saline (or water) is introduced into the lower rectum of the patient via a moulded tubular plastic fitting (e.g. 50-80 mm long, 5-8 mm diameter) on the nozzle end of a syringe. The fitting is designed to pass the liquid via many peripheral holes along its furthermost 25-40 mm (i.e. the tip end), so that the wash fluid is directed onto the inner walls of the GI tract of the patient. The wash fluid is then aspirated using the syringe to collect the fluid sample. A filter material is located in the tubular fitting (e.g. Dacron windings, as used in the head of a swab), so that the withdrawn aspirate is filtered and reasonably clear. After withdrawal of the sample, the tubular fitting is discarded and the withdrawn aspirate removed from the syringe to be used for testing for occult blood.

FOB testing of the sample obtained by this procedure is conducted using a testing device as

disclosed in International Patent Application No. PCT/AU98/00830 (WO 99/18436) configured to enable both a guaiac test and an immunochromatographic test for haemoglobin to be carried out on the same sample.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

CLAIMS:

1. A method for collecting a sample from a patient, which comprises collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient.

2. A method according to claim 1, wherein said sample is collected intra-rectally from the patient by a lower rectal lavage or wash procedure.

3. A method according to claim 2, wherein a wash fluid is introduced into the lower rectum to wash the inner wall of the gastrointestinal tract, and the wash fluid is subsequently aspirated and collected as the sample for subsequent testing.

4. A method according to claim 3, wherein the wash fluid is selected from water and saline, and optionally further includes compatible surfactants and/or buffers.

5. A method according to claim 1, wherein said sample is collected intra-rectally from the patient by means of a swab, brush or similar collecting device.

6. A method for detecting a pathological condition or disease in the gastrointestinal tract of a patient, which comprises the steps of:
   (i) collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient; and
   (ii) detecting the presence in the sample, if any, of an analyte indicative of the pathological condition or disease.

7. A method according to claim 6, wherein said sample is collected intra-rectally from the patient by a lower rectal lavage or wash procedure.

8. A method according to claim 7, wherein a wash fluid is introduced into the lower rectum to wash the inner wall of the gastrointestinal tract, and the wash fluid is subsequently aspirated and collected as the sample for subsequent testing.

9. A method according to claim 8, wherein the wash fluid is selected from water and saline, and optionally further includes compatible surfactants and/or buffers.

10. A method according to claim 4, wherein said sample is collected intra-rectally from the patient by means of a swab, brush or similar collecting device.

11. A method according to any of claims 4 to 10, wherein the pathological condition is colorectal cancer, and said analyte is occult blood.

12. A method according to claim 11, wherein the presence in the sample of occult blood, if any, is detected by (a) a guaiac- or other chromogen-based test for haemoglobin, or (b) an immunochromatographic assay for haemoglobin, or (c) a combination of (a) and (b).

13. A method according to any of claims 4 to 10, wherein said collected sample comprises cells and/or cell debris, and said sample is subjected to cytological examination.

14. A method according to claim 13, wherein said cells and/or cell debris are examined for DNA, RNA or protein markers of a pathological condition or disease.

15. A method for detection of occult blood as indicative of a pathological condition or disease in the gastrointestinal tract of a patient, which comprises the steps of:

(i) collecting a sample directly from the lumen of the lower gastrointestinal tract of the patient; and

(ii) detecting the presence of blood, if any, in the sample indicative of the pathological condition or disease by (a) a guaiac- or other chromogen-based test for haemoglobin, or (b) an immunochromatographic assay for haemoglobin, or (c) a combination of (a) and (b).

16. A method according to claim 15, wherein said sample is collected intra-rectally from the patient by a lower rectal lavage or wash procedure.

17. A method according to claim 16, wherein a wash fluid is introduced into the lower rectum to

wash the inner wall of the gastrointestinal tract, and the wash fluid is subsequently aspirated and collected as the sample for subsequent testing.

18. A method according to claim 17, wherein the wash fluid is selected from water and saline, and optionally further includes compatible surfactants and/or buffers.

19. A method according to claim 15, wherein said sample is collected intra-rectally from the patient by means of a swab, brush or similar collecting device.

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/AU02/00419**

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl. [7]: A61B 10/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

REFER ELECTRONIC DATABASE DETAILED BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI and JAPIO IPC A61B 10/- and keywords sampl:, biops:, rectal, rectum, colon, gastro:, anal:, anus:, cancer, disease, tumor, tumour, antigen:, detect, screen, diagnos:

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P, X | WO 01/74251 A2 (RITA MEDICAL SERVICES INC) 11 October 2001<br>Page 8, line 3 to Page 10, line 5 and Figure 1 | 1, 6, 15 |
| X | WO 98/41153 A1 (A+ SCIENCE INVEST AB) 24 September 1998<br>Whole document | 1, 6, 15 |
| A | CA 2123856 A1 (FAGERHOL) 28 November 1994<br>Whole document | |

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>E-mail address: pct@ipaustralia.gov.au<br>Facsimile No. (02) 6285 3929 | **COLIN FITZGIBBON**<br>Telephone No : (02) 6283 2226 |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
**PCT/AU02/00419**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent Document Cited in Search Report | | Patent Family Member | | | | | |
|---|---|---|---|---|---|---|---|
| WO | 01/74251 | AU | 200149752 | AU | 200151134 | US | 2002026127 |
| | | US | 2002026188 | WO | 01/74252 | JP | 2001272697 |
| | | US | 2001026331 | | | | |
| WO | 98/41153 | AU | 64315/98 | | | | |
| CA | 2123856 | US | 5455160 | | | | |

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