



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b>  <b>A61K 49/02</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 91/08777</b>  <b>(43) International Publication Date:</b> 27 June 1991 (27.06.91)
<b>(21) International Application Number:</b> PCT/BR90/00022 <b>(22) International Filing Date:</b> 17 December 1990 (17.12.90) <b>(30) Priority data:</b> 8906497 15 December 1989 (15.12.89) BR <b>(71) Applicants (for all designated States except US):</b> FUNDAÇÃO OSWALDO CRUZ (FIOCRUZ) [BR/BR]; Av. Brasil no. 4365, Manguinhos, 21040 Rio de Janeiro, RJ (BR). UNIVERSIDADE FEDERAL DE PERNAMBUCO [BR/BR]; Av. Moraes Rego no. 1235, Cidade Universitária, 50730 Recife, PE (BR). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> DREYER VIEIRA, Gerusa [BR/BR]; Rua Ada Vieira no. 144, Casa Forte, 52060 Recife, PE (BR). MARCHETTI BARRETO CRUZ, Fernanda [IT/BR]; Rua dos Navegantes no. 1353, Apt. 1402, Boa Viagem, 51020 Recife, PE (BR). CARMO NETO GOMES, Solange do [BR/BR]; Rua Afonso Batista no. 172, Apto 102, Espinheiro, 52051 Recife, PE (BR).		<b>(81) Designated States:</b> AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHOD FOR UTILIZATION OF LYMPHOSCINTIGRAPHY IN ESSENTIALLY FUNCTIONAL BUT ALSO MORPHOLOGICAL ANALYSIS OF BOTH DEEP AND SUPERFICIAL LYMPHATIC SYSTEMS THROUGH STATIC AND/OR SEQUENTIAL IMAGES  <b>(57) Abstract</b>  <p>Method to obtain both functional as well as morphological map of Superficial and/or Deep Lymphatic Systems, since inferior members till thorax duct of both symptomatic or asymptomatic but with the potentiality to develop lymphatic pathology individuals allowing preventive diagnosis. Said map is obtained through lymphoscintigraphy method by injecting at the proper site the 99mTc-Dex 500 radiopharmaceutical composition. After injections the patient is submitted to an adequate lymphatic flow stimulation physiological factor followed by his lymphatic system images collection using a large-field-of-view gamma camera provided with parallel collimator for high resolution and low power, in line with a computer. They may be sequential or static, by successive sections, images.</p>		

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"METHOD FOR UTILIZATION OF LYMPHOSCINTIGRAPHY IN  
ESSENTIALLY FUNCTIONAL BUT ALSO MORPHOLOGICAL ANALYSIS OF  
BOTH DEEP AND SUPERFICIAL LYMPHATIC SYSTEMS THROUGH STATIC  
AND/OR SEQUENTIAL IMAGES"

05 BACKGROUND OF THE INVENTION

The present invention refers to the obtaintion  
process of Superficial and/or Deep Lymphatic Systems  
functional as well as morphologycal map, since inferior  
members until thorax duct of both symptomatic or  
10 asymptomatic with the potentiallity to develop lymphatic  
pathology individuals.

Among other lymphatic pathologies as neoplasies for  
example, lymphatic edema of inferior members in human  
beings represents until this moment a special diagnosis  
15 challenge, of which principal strangulation falls over the  
technic limitations of diagnostic approach used to study  
those systems. The lymphoangiography, a radiologic method  
used in the majority of limphatic investigation centers  
is limited for numberless factors, being the most  
20 important, the fact of potentially be able to damage the  
examined vein, sometimes, irreversivable. This iatrogenic  
possibility has limited the number of patients to be  
investigated, turning on impracticable the preventive  
diagnosis of asymptomatic with potential edema  
25 development and even posterior inferior members  
elephantiasis individuals. That refered impracticability  
for asymptomatic individuals, is still more remarkable in  
the access to normal individuals, that represents an  
essential step for the pathologic modifications proper

interpretation, which knowledge is still not exhausted.

All of that methodology limitations and unwish consequences, went on to the search of new technics that should make possible those systems more adequate study.

05 Then appeared the radiopharmacs, to be used in lymphoscintigraphy technics. Initially, the colloidal  $^{198}\text{Au}$ , in general gave a good kind of lymphoscintigraphy, but its use has been abandoned because of the high absorbed radiation at the injection site.

10 Among the  $^{99\text{m}}\text{Tc}$  marked compounds proposed for lymphoscintigraphy, such as phytats, hematies, albumin and colloids, only the antimonial colloid showed satisfactory proprieties in relation to the visualization map of lymphonodes metastasis of patients with mamma's carcicoma  
15 and melanome.

Although the encouraging related results, two great limitations remains for the use of  $^{99\text{m}}\text{Tc}$  marked colloids, mainly due to particular characteristics of the used tracers: 1 - The interstitial space clearence and  
20 its lymphatic flow entering depends on the particle size and the mononuclear phagocitic system functional state; 2 - The tracer migration from injection interstitial site is only 1-35% in 24 hours, not reflecting this way, the lymphatic vessel flux.

25 Then, one tracer not particled, not colloidal, lymph soluble and with large enough molecules not to penetrate in capillary membrane after interstitial applying, would be the desireble substance to lymphoscintigraphy purpose(1).

In 1982, Henze and cols.(1) presented a new  $^{99m}\text{Tc}$ -Technetium radiopharmac: the  $^{99m}\text{Tc}$ -Dextran, that was first utilized as sanguine pool marker in angiocardigraphyc studies and soon after, for lymphoscintigraphy.

Being the Dextran a glucose polymer clinically used as plasmatic expensor, innocuos, that stays in the vascular space after endoveinous injection applying, that has an adequate molecular weight not to cross capillary vessels, being consequently drained only by lymphatic system, besides don't be phagocited, it permitted its utilization with sucessful possibilities.

In 1984, Ceriane and cols.(2) also used the 500000 molecular weight  $^{99m}\text{Tc}$  - Dextran in abdominal lymphoscintilographyc studies of control individuals and patients with lymphom and elephantiasis. Their objective was visualize the popliteal, inguinal, iliac and lomboaortic localizations corresponding lymphonodes.

The lymphatic phylariasis is a desease caused by *Brugia* and *Wuchereria* species, that attains around 80 million persons and exposes people to a great infection risk. The *Wuchereria bancrofti* causes the bancroftose and revests itself of a greater importance such for the number of people attained as for the fact of being an exclusive human being desease.

The lack of an experiment animal turns impossible a great number of studies, in all fields, difficulting and retarding a profounded knowledge about that desease, which is a large clinic spectre one with difficult diagnostic

and most of times, impossible prognostic. As it is a parasite that is lodged in the lymphatic system, the principal diseases's consequence is this system's damage. So, it was necessary to develop protocols for the  
05 lymphatic attacking precocious detection, before the symptomatology appearing, which once installed is very difficult to solve, when it is possible to do that.

The clinic form that represents a greater challenge to the investigators logic is exactly the circle  
10 microphilarian one, that in most part of individuals appears completely asymptomatic.

Until today, it was never done a longitudinal study that could characterize the natural diseases's evolution, allowing that way an individual prognostic. With the  
15 investigation protocol proposed by the present invention, it was possible to obtain a clear and precise evaluation of lymphatic system functionality in potentially predisposed individuals. Because of the complete asymptomaticity of those individuals, although lodging the  
20 parasite, any investigation was initiated only by the lymphatic edema appearing occasion, don't being ventilated before that they could have some modifications in their lymphatic draining system and what does it mean. The precocius diagnosis was been ever retarded.

#### 25 DETAILED DESCRIPTION OF THE INVENTION

The adequate radiopharmaceutical composition was prepared by mixing 2 or 3ml of  $^{99m}\text{Tc}$ -sodic pertechnetate (2600MBq/ml), freshly eluted from a Technetium generator, with 100mg of leiophyllized dextran with a standard

molecular weight that may vary from about 100.000 to 500.000. The chosen one was the 500.000 daltons dextran, so that it was obtained the <sup>99m</sup>Tc-Dex 500 radiopharmaceutical composition.

05 That solution was utilized in an appropriate injection within the next six hours. The injection used was an insulin pattern syringe provided with a 13x0,36mm (27,56) needle, with single body in order to avoid dead space breeding, containing one aliquot of said solution. The  
10 injection syringe was calibrated by means of a curiometer in order to consist for each inferior extremity of 0,3ml (delta volume: 0,2-0,4 ml) of <sup>99m</sup>Tc-Dex 500 with activity of 185 MBq (delta activity: 150-220 MBq) and 7,5mg (delta: 5-10mg) of dextran 500.000.

15 The injection applying is subcutaneous and in order to take Deep Lymphatic System images, said applying is done at exterior retrómalleolar region, one for each side, but to obtain Superficial Lymphatic System images, the injection applying is done at foot's first interdigital  
20 space, in the direction of its upper part, one for each side too.

Immediately after injections applying the patient is submitted to an adequate lymphatic flow stimulation physiological factor. In order to obtain sequential  
25 images, the injections are applied with the patient at supine position under the equipment that will take the images and his lymphatic system is stimulated by a passive nature exercise that consists in contemporaneous massage over injection site during 3 minutes. By the other

hand, to obtain static images, the injections are applied with the patient at dorsal decubitus man position and his lymphatic system is stimulated by an appropriate up and down walking, done in conformity to his own rhythm, bare-footed, along a course around 350 to 450 meters.

The equipment used to take the images is a large-field-of-view gamma camera provided with parallel collimator for high resolution and low power, in line with a computer. In order to obtain sequential images the machine is placed at anterior incidence over patient's pelvic region and the images are collected sequentially at about 1 minute intervals during the first hour, being registered, each one, in a 64x64 pixels matrix, automatically kept in floppies disks and analysed by the computer, both visual and quantitatively, through an activity versus time curve since interest analog areas settled down by means of an electronic pen pointed over them. However, to obtain static images, they are taken by successive sections with the machine placed at anterior incidence over patient's inferior members, pelvis, abdomen and thorax, being registered, each one, in a 128x128 pixels matrix during 10 minutes or untill reach 100000 countings for image and then automatically kept in floppies disks for posterior analysis. In this case, the images are collected at about 1 hour, 3 hours and, if necessary, 24 hours intervals.

#### DISCUSSION OF THE INVENTION

The assymptomatic individuals investigation with the presente method revealed the unknown fact that some of

them have already developed significative alterations in their lymphatic system with no manifest symptom at all.

What can modify the lymphatic lesion course? The therapeutics, the individual responses or these two  
05 factors combination?

This technic's innocuity permits its procedures repetition so many times as necessary to allow a longitudinal study with adequate individual time intervals. Otherwise, the thecnic's good reproducibility  
10 permits an uniform interpretation over the same patient, as well as among diferent ones.

Besides Superficial Lymphatic System visualization with both normal and abnormal images, Deep Lymphatic System was also investigated by lymphoscintigraphy method, that  
15 had never been used for this purpose before.

By the results qualitative analysis it was verified the necessity of a semiquantitative study. Then, it was procceded to the obtaintion of standarded time intervals images, that permitted a lymphatic system function dynamic  
20 study, inexplored till nowadays.

Many study possibilities come from this method, for example:

1) Normal individuals Lymphatic Systems physiology studies, providing basic informations for these systems' morbid processes comprehension.  
25

2) Preventive diagnosis of individuals with the potentiallity to develop lymphatic pathology, such in infeccious, parasitic, neoplastic as in bad formation processes.

- 3) Longitudinal studies allowing prognostic possibilities.
- 4) Therapeutic conducts monitoration allowing the necessary adjustments during each pathology specific therapy.
- 05 5) Deep Lymphatic vessels exploration with static and/or dinamyc images, allowing qualitative and semiquantitative analysis.
- 6) Superficial Lymphatic System exploration with dinamyc images, allowing semiquantitative analysis.

ADVANTAGES OF LYMPHOSCINTIGRAPHY  
IN RELATION TO TRADITIONAL  
LYMPHOGRAPHY

LYMPHOSCINTIGRAPHY	TRADITIONAL LYMPHOGRAPHY
1) Isotopic Method	1) Radiologic Method
2) Ambulatory patient	1) Hospitalized patient
3) Injection (subcutaneous or intradermic)	3) Cannulation (under pressure introduction)
4) Without pain Without lymphangitis	4) Local anesthesia
5) Immediate discharge from hospital, allowed routine activities	5) 24 to 48 hours rest
6) None known reaction	6) Eventual lymphangitis Eventual allergic reaction Eventual incision infection Eventual lymphatic rupture
7) Functional and morphological analysis	7) Only morphological analysis
8) Low radiation dose	8) High radiation dose
9) Qualitative and Semiquantitative results	9) Only qualitative results
10) May be repeated as much as necessary	10) 2 times maximum
11) Low Cost / Benefit	11) High Cost / Benefit
12) Routine examination	12) Special circumstances: When a morphological determination is important and surgery is planned

## CASUISTRY

Number of patients: 46

Lymphatic System Examination:

a) Superficial:  $46 \times 2 = 92$  legs

05 b) Deep:  $23 \times 2 = 46$  legs

Total of examinations: 138 legs

Dynamic: 3 patientes

Superficial:  $2 \times 2 = 4$

Deep:  $1 \times 2 = 2$

10 Total: 6

General total:  $138 + 6 = 144$

## INTERPRETATION

1) In the lymphatic flux appreciation of inferior members it was considered normality/abnormality parameters at  
15 superficial/deep lymphoscintigraphy utilizing the  $99\text{ m Tc}$ -dextran radiopharmaceutical composition, the following characteristics:

## 1.1) SUPERFICIAL

a) **Normality:** rectilineal superficial vessels  
20 visualization since inferior saphena lymphatic duct till superficial inguinal lymphonodes. They must be symmetric in number and visualization intensity. Follows the parailiac and paraortic lymphonodes chain (inverted Y) visualization. All these structures must be visualized  
25 until 3 hours at maximum, after radiopharmaceutical injection.

b) **Abnormality:** multiple tortuous or dilated vessels, along the leg and/or the thigh, collaterals presence, dermic reflow, popliteal lymphonodes absence, flux absence

-11-

or decrease, any level flux stop persistent after 3 hours since radiopharmaceutical injection (checked with 24 hours images).

#### 1.2) DEEP:

05 a) **Normality:** active rectilineal vessels visualization, along the exterior saphena lymphatic duct that connect to deep system through popliteal lymphonodes. These lymphonodes must be visualized and they are usually symmetric in number and imaging intensity. Follows the  
10 inguinal ganglial, iliac and aortic chains.

b) **Abnormality:** similar to superficial system, tortuous or dilated vessels, collaterals presence, dermic reflow, flux absence or decrease, popliteal lymphonodes absence, any level flux stop, since leg till abdomen, are considered  
15 abnormalities.

#### RADIOPHARMACEUTICAL STABILITY

Thyroid non visualization serves as "in vivo" radiopharmaceutical integrity quality control.

- 1) Henze, E., Schelbert, H.R., Collins, J.D., Najafi, A.,  
20 Barrio, J.R., Bennett, L.R. - Lymphoscintigraphy with Tc-99m - Labeled Dextran - J. Nucl. Medicine 23: 923-929, 1982.
- 2) Ceriani, J., Caneda, G., Argüelles, M.G., Canellas, C.O., Rozados, I., Mitta, A.E.A. - El Dextrano X 500. 99mTc en  
Linfocentellografia Abdominal - Acta Bioquímica Clínica  
25 Latinoamericana, Vol. XVIII, number 2, 345-351, 1984.

## CLAIMS

1) Method for utilization of lymphoscintigraphy in essentially functional but also morphological analysis of Deep Lymphatic System through static and/or sequential  
05 images, of Superficial Lymphatic System through sequential images and of asymptomatic microfilaremic individuals' Superficial Lymphatic System through static images, comprising the following steps:

a) The adequate radiopharmaceutical preparation by mixing  
10 2 or 3 ml of  $^{99m}\text{Tc}$  - sodic pertechnetate (2600 MBq/ml), freshly eluted from a Technetium generator, with 100 mg of leiophyllized dextran with an acceptable molecular weight, contained in a multidose ampoule.

b) Aliquots of step "a" solution utilization in an  
15 appropriate injection, within the next six hours.

c) Appropriate calibration of step "b" injection syringe by means of a curiometer.

d) Step "c" injection applying at the correct site, by the appropriate way, with the patient at the adequate  
20 position.

e) Patient's applying of a lymphatic flow stimulation physiological factor, immediately after injection.

f) Patient's adequate lymphatic flow images collection, by means of an appropriate equipment, after lymphatic flow  
25 stimulation.

2) Method for utilization of lymphoscintigraphy, according to claim 1, wherein step "a" said dextran's molecular weight is standardised and may vary from about 100.000 to 500.000.

3) Method for utilization of lymphoscintigraphy, according to claim 2, wherein is used the dextran of 500.000 daltons to obtain the  $^{99m}\text{Tc}$ -Dex 500 radiopharmaceutical composition.

05 4) Method for utilization of lymphoscintigraphy, according to claim 1, wherein step "b" the injection used is an insulin pattern syringe provided with a 13 x 0,36 mm (27,5 G) needle, with single body in order to avoid dead space breeding, containing in each syringe one aliquot of step  
10 "a" solution.

5) Method for utilization of lymphoscintigraphy, according to claim 1, wherein step "c" the syringe's calibration consists for each inferior extremity of 0,3 ml (delta volume : 0,2 - 0,4 ml) of  $^{99m}\text{Tc}$ -Dex 500 with activity of  
15 185 MBq (delta activity: 150 - 220 MBq) and 7,5 mg (delta: 5-10 mg) of dextran 500 000.

6) Method for utilization of lymphoscintigraphy, according to claim 1, wherein step "f" the equipment used is a large-field-of-view gamma camera provided with parallel  
20 collimator for high resolution and low power, in line with a computer.

7) Method for utilization of lymphoscintigraphy, according to claim 1, where in order to obtain the static Deep Lymphatic System images, in step "d" the injection is  
25 applied subcutaneously at exterior retromalleolar region, one for each side, with the patient at dorsal decubitus position; in step "e" the lymphatic flow stimulation physiological factor is a patient's appropriate up and down walking, after bilateral radiopharmaceutical applying

and, in step "f" the images are collected adequately at about 1 hour, 3 hours and, if necessary, 24 hours intervals after injection.

05 8) Method for utilization of lymphoscintigraphy, according to claim 7, wherein the patient's up and down walking is done in conformity to his own rhythm, bare-footed, and along a course around 350 to 450 meters.

9) Method for utilization of lymphoscintigraphy, according to claim 7, wherein the images are collected by successive  
10 sections, with the machine at anterior incidence over patient's inferior members, pelvis, abdomen and thorax, being registered, each one, in a 128 x 128 pixels matrix during 10 minutes or untill reach 100 000 countings for image and then automatically kept in floppies disks for  
15 posterior analysis.

10) Method for utilization of lymphoscintigraphy, according to claim 1, where in order to obtain the sequential Deep Lymphatic System images, in step "d" the injection is applied subcutaneously at exterior  
20 retromalleolar region, one for each side, with the patient at supine position under the equipment that will take the images; in step "e" the lymphatic flow stimulation physiological factor is an appropriate passive nature exercise, after bilateral radiopharmaceutical applying  
25 and, in step "f" the images are collected adequately at about 1 minute intervals during the first hour.

11) Method for utilization of lymphoscintigraphy, according to claim 10, wherein the passive nature exercise used is contemporaneous massage over injection site during

3 minutes.

12) Method for utilization of lymphoscintigraphy, according to claim 10 wherein the images are collected sequentially, with the machine at anterior incidence over patient's pelvic region, being registered, each one, in a 64x64 pixels matrix, automatically kept in floppies disks and analysed by the computer, both visual and quantitatively, through an activity versus time curve since interest analog areas settled down by means of an electronic pen pointed over them.

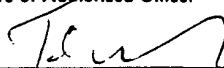
13) Method for utilization of lymphoscintigraphy, according to claim 1, where in order to obtain the sequential Superficial Lymphatic System images, in step "d" the injection is applied subcutaneously at foot's first interdigital space, in the direction of its upper part, one for each foot, with the patient at supine position under the equipment that will take the images; in step "e" the lymphatic flow stimulation physiological factor is an appropriate passive nature exercise as described in claim 11, after bilateral radiopharmaceutical applying and, in step "f" the images are collected as described in claims 10 and 12.

14) Method for utilization of lymphoscintigraphy, according to claim 1, where in order to obtain the static asymptomatic microfilaremic individuals' Superficial Lymphatic System images, in step "d" the injection is applied subcutaneously at foot's first interdigital space, in the direction of its upper part, one for each foot, with the patient at dorsal decubitus position; in step "e"

the lymphatic flow stimulation physiological factor is a patient's appropriate up and down walking as described in claim 8, after bilateral radiopharmaceutical applying and, in step "f" the images are collected as described in  
05 claims 7 and 9.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/BR 90/00022

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. <sup>5</sup> : A 61 K 49/02		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. <sup>5</sup>	A 61 K 49/00, 43/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> *		
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	Chemical Abstracts, Volume 101, no. 19, issued 1984, November 5 (Columbus, Ohio, U.S.A.), J. Ceriani et al. "Technetium-99m. Dextran X 500 in abdominal lymphoscintillography", see page 306, column 1, the abstract-no. 166 433x, Acta bioquim.Clin.Latinoam. 1984, 18(2),345-51 (Span.). ---	(2,3)
X	Chemical Abstracts, Volume 98, no. 19, issued 1983, May 9 (Columbus, Ohio, U.S.A.), E. Henze et al. "Kinetics of technetium-99m-labeled dextran a new radiopharmaceutical for radionuclide lymphangiography and blood pool imaging", see pages 213, 214, the abstract-no. 157 195p, Nucl.Med.Biol. Adv., Proc.World Congr., 3rd 1982 (Pub.1983), 1,444-7 (Eng.). ---	(2,3)
<p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
12 February 1991 (12.02.91)		20 February 1991 (20.02.91)
International Searching Authority		Signature of Authorized Officer
AUSTRIAN PATENT OFFICE		

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Chemical Abstracts, Volume 110, no. 25, issued 1989, June 19 (Columbus, Ohio, U.S.A.), K. Wingaardh et al. "Evaluation in vitro and in vivo of two labeling techniques of different <sup>99m</sup> Tc-dextran for lymphoscintigraphy", see page 288, column 1, the abstract no. 227 758s, Eur.J.Nucl.Med. 1989,15(3), 146-51 (Eng).	(2,3)
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V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1, 4-14 because they relate to subject matter not required to be searched by this Authority, namely:

Diagnostic method practised on the human or animal body  
Article 17(2)(b)iv

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.