



Universiteit
Leiden
The Netherlands

ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis

Lind van Wijngaarden, R.A.F. de

Citation

Lind van Wijngaarden, R. A. F. de. (2009, March 12). *ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis*. Retrieved from <https://hdl.handle.net/1887/13612>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/13612>

Note: To cite this publication please use the final published version (if applicable).



Appendix I

Affiliations



Leiden University Medical Center, the Netherlands

Department of Pathology

Robert A.F. de Lind van Wijngaarden

Ingeborg M. Bajema

Leendert van Rijn

Emile de Heer

Jan A. Bruijn

Department of Medical Statistics

Ron Wolterbeek

Department of Cardiology

Herbert A. Hauer (formerly VU Medical Center, department of Cardiology)

Meander Medical Center, Amersfoort, the Netherlands

Department of Internal Medicine

E. Christiaan Hagen

Addenbrooke's Hospital, Cambridge University, United Kingdom

Renal Unit

David R.W. Jayne

Oliver Floßmann

University Hospital of Malmö, Sweden

Department of Nephrology

Kerstin W. Westman

Hammersmith Hospital, London, United Kingdom

West London Renal and Transplant Centre

Gill Gaskin

Charles D. Pusey

Rigshospitalet, Copenhagen, Denmark

Department of Otolaryngology

Niels Rasmussen



Affiliations

Hôpital Necker, Paris, France

INSERM U507

Laure-Hélène Noël

Ospedale San Carlo Borromeo, Milan, Italy

Renal Immunopathology Center

Franco Ferrario

University of Heidelberg, Germany

Department of Pathology

Rüdiger Waldherr

University of East Anglia, Norwich, United Kingdom

School of Medicine, Health Policy and Practice

Richard A. Watts

Spedali Civili, University of Brescia, Italy

Department of Nephrology

Gina Gregorini

University Hospital Maastricht, Maastricht, the Netherlands

Department of Clinical and Experimental Immunology

Jan Willem Cohen Tervaert

Hôpital Cochin, Paris, France

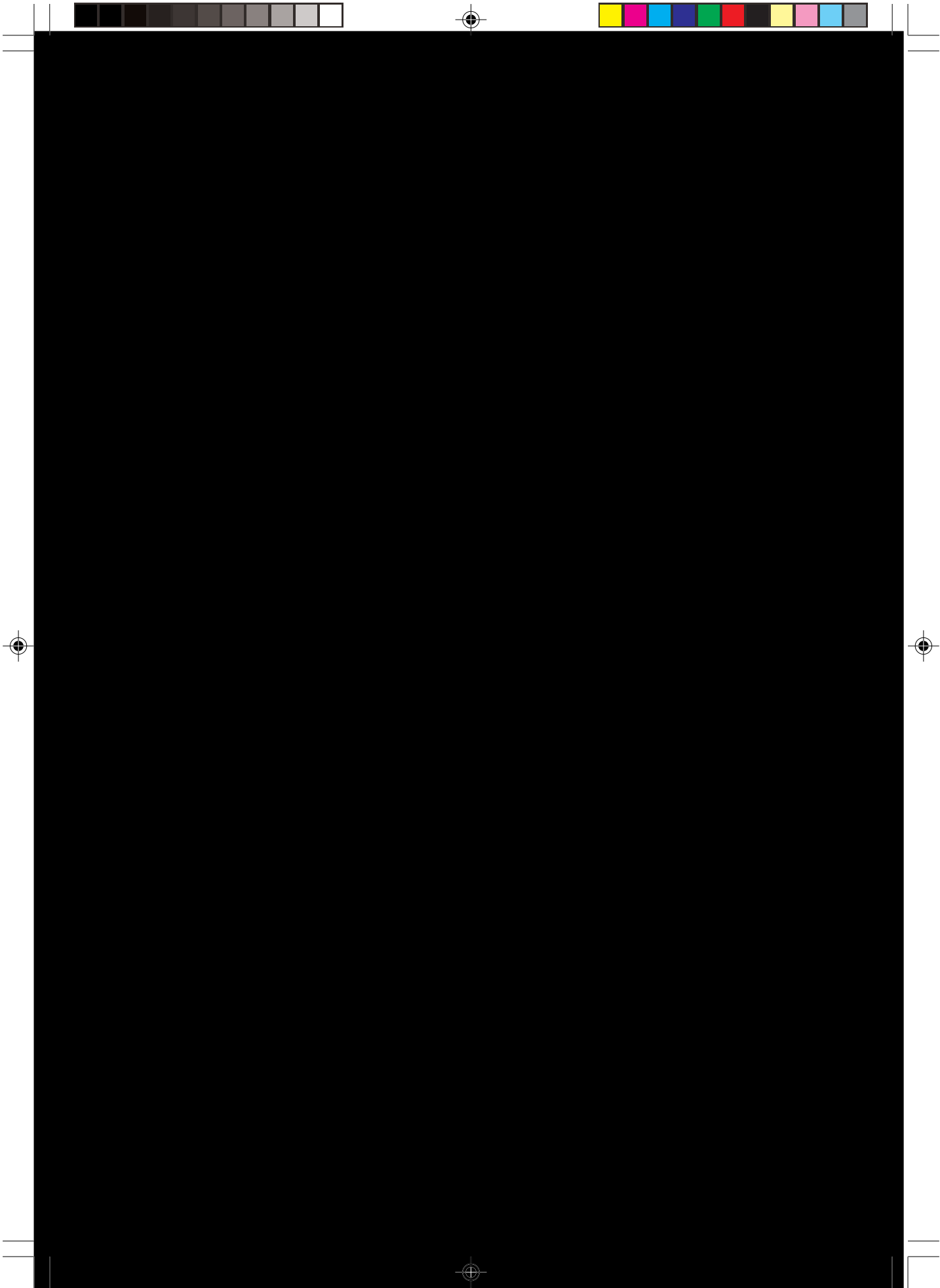
Department of Internal Medicine

Alfred D. Mahr

Massachusetts General Hospital, Boston, United States

Department of Medicine

John L. Niles





Appendix II

Scoring form





NON-GLOMERULAR LESIONS

Interstitialium	
edema	-/+
infiltrates ⁸	-/+ /++ /+++
celltype of infiltrate ⁹	
neutrophils	-/+ /++
mononuclear cells	-/+ /++
eosinophils	-/+ /++
fibrosis ¹⁰	-/+ /++
granulomas ¹¹	

Vessels¹⁴	
small vessels	large vessels
vasculitis ¹⁵	present
arteries	vasculitis ¹⁵
	sclerosis ¹⁶
present	
sclerosis ¹⁶	
	arterioles
	sclerosis ¹⁶
	thrombosis ¹⁷

Comments/Diagnosis:

Tubules	
casts	-/+
necrosis	-/+
atrophy ¹²	-/+ /++
intra-epithelial infiltrate ¹³	-/+



Appendices

Definitions

Fibrinoid necrosis	Clear location of fibrin or fibrinoid material inside the glomerulus
Total nr. of glomeruli	The maximal number of glomeruli in one of the sections without glomeruli in the edge
Crescents	Extracapillary lesions
Circumferential	> 50% of Bowman's space
Segmental	< 50% of Bowman's space
Cellular	Includes purely cellular and fibrocellular crescents
Fibrous	Fibrotic (sclerotic) lesion with fibroblasts filling Bowman's space
Sclerosis	Only scored in glomeruli that do not show extracapillary proliferation
Local	Small rounded area of scarring within the flocculus (< 20% of the glomerulus)
Segmental	> 20% and < 80% of the glomerulus sclerosed within the flocculus
Global	> 80 % of the glomerulus sclerosed
Synechia	Small fibrous adhesion of the flocculus with Bowman's capsule without proliferation of sclerosis
Periglomerular infiltrate	Dense infiltrate around a glomerulus without granuloma (with or without destruction of Bowman's capsule) excluding global glomerular sclerosis. The amount of cells has to be more than in the surrounding interstitium
Granulomatous reaction	Destruction of the glomerulus with an accumulation of epitheloid cells with or without giant cells around the glomerulus
Interstitial infiltrate	
-	No infiltrate
+	Mild infiltrate
++	Quite dense infiltrate
+++	Very dense infiltrate



Scoring form

Cell type of infiltrate

- | | |
|----|------------------------------------|
| - | Cell type not present |
| + | Cell type is present |
| ++ | Cell type is predominantly present |

Fibrosis

- | | |
|----|-------------------------------|
| - | No fibrosis |
| + | Focal interstitial fibrosis |
| ++ | Diffuse interstitial fibrosis |

Interstitial granulomas

Accumulation of epithelioid cells with or without giant cells without glomerular remnants (count the number of granulomas in the biopsy); may occur in perivascular, periglomerular, and peritubular location

Tubular atrophy

- | | |
|----|-------------------------------|
| - | No atrophy |
| + | Small foci of tubular atrophy |
| ++ | Extensive tubular atrophy |

Intra-epithelial infiltrate

Marked infiltrate present in the tubular epithelium (tubulitis)

Vessels

- | | |
|-----------|--|
| Artery | Vessel > Ø of tubules in the biopsy and < large vessel |
| Arteriole | Vessel < Ø of tubules in the biopsy |

Vasculitis

Marked vessel lesions with necrosis or necrosis and infiltrates

Sclerosis

Intima fibrosis/splitting of the elastical membrane/decrease of lumen size/calcification/vessel wall scarring

Thrombosis

Total occlusion with fibrin



People often say that motivation doesn't last.
Well, neither does bathing: that's why we recommend it
daily.
Zig Ziglar



Appendix III

Curriculum vitae



De auteur van dit proefschrift werd op 16 juli 1980 geboren te 's-Gravenhage. Na het behalen van het gymnasiumdiploma aan het Christelijk Gymnasium Sorghvliet te 's-Gravenhage in 1998, startte hij datzelfde jaar met de studie Biomedische Wetenschappen aan de Universiteit van Antwerpen in België. In 1999 begon hij met de studie Geneeskunde aan de Universiteit Leiden. De eerste ervaringen met wetenschappelijk onderzoek werden vanaf eind 2000 opgedaan, toen hij begon met onderzoek naar ANCA-geassocieerde vasculitis op de afdeling Pathologie (hoofd: prof. dr. G.J. Fleuren), onder leiding van mw. dr. I.M. Bajema en prof. dr. J.A. Bruijn. Dit project raakte in een stroomversnelling toen hij een beurs voor het excellente studenten-traject kreeg en mondde later uit in dit proefschrift. Zijn studie werd onderbroken toen hij een jaar voorzitter was van de Medische Faculteit der Leidse Studenten (M.F.L.S.) en toen hij van begin 2004 tot halverwege 2005 full-time tijd besteedde aan zijn onderzoek. Tijdens zijn studie bekleedde hij functies in een twintigtal commissies die gevarieerd van aard waren, maar allemaal als doel hadden het medisch onderwijs binnen het Leids Universitair Medisch Centrum (LUMC) of in heel Nederland te verbeteren, te verbreiden of te veraangename. Zo heeft hij in de commissie gezeten die de intracurriculaire uitwisseling met het Karolinska Instituut in Stockholm, Zweden, heeft opgezet en was hij voorzitter van een commissie voor curriculumexploratie aan de Harvard Medical School in Boston, VS. In september 2005 begon hij met de co-schappen en als bestuurslid van het Landelijk Overleg Co-Assistenten (LOCA) en de Leidsche Co-assistenten Raad (LCR), waar hij later voorzitter van werd. Momenteel is hij lid van de Commissie Herziening Raamplan, die de eindtermen voor de Nederlandse artsopleidingen opstelt. De artsenbul werd behaald in oktober 2007. Na zijn artsexamen is hij werkzaam geweest als arts-assistent Heelkunde in het Bronovo Ziekenhuis te 's-Gravenhage (opleider: dr. H.J. Smeets). Sinds januari 2008 is hij werkzaam als arts-assistent Cardio-Thoracale Chirurgie in het Academisch Medisch Centrum (AMC) te Amsterdam (hoofd: prof. dr. mr. dr. B.A.J.M. de Mol) en sinds februari 2009 in het Erasmus Medisch Centrum te Rotterdam (hoofd: prof. dr. A.J.J.C. Bogers).



The author of the thesis was born on July 16, 1980 in The Hague, the Netherlands. After completing his high school on a gymnasium level at the Christian Gymnasium Sorghvliet in The Hague in 1998, he studied Biomedicine at the University of Antwerp in Belgium. In 1999, he commenced his medical study at Leiden University, the Netherlands. His first experiences in scientific research date back from the end of 2000, when he started his research on ANCA-associated vasculitis at the Department of Pathology (head: prof. dr. G.J. Fleuren), under the guidance of dr. I.M. Bajema and prof. dr. J.A. Bruijn. This project took off when he was awarded the scholarship for excellent students and later on, resulted in this thesis. His study was interrupted when he was elected president of the Leiden Medical Students' Association (M.F.L.S.) for one year and when he was a full-time researcher from the spring of 2004 until the fall of 2005. During his medical training he resided in over 20 committees of a variety in nature, but the purpose of all of which was to improve or to broaden medical education, or to make it a more joyful experience, both in the Leiden University Medical Center (LUMC), and in the Netherlands as a whole. In this setting, he held a position in the committee which effectuated the intracurricular exchange between the LUMC and the Karolinska Institute in Stockholm, Sweden. Moreover, he chaired the committee that carried out a curricular exploration at the Harvard Medical School in Boston, USA. In September of 2005 he started his clinical rotations and occupied positions in the Dutch National Board of Students in Clinical Rotations and its local organization in Leiden, which he later presided for over a year. Currently, he is a member of the Committee for Reviewing the Masterplan, which determines the terms that have to be met by all medical schools in the Netherlands to educate future physicians. He received his MD degree in October 2007. Since then, he has been a resident in general surgery at the Bronovo Hospital in The Hague (mentor: dr. H.J. Smeets). Since January 2008, he has been a resident in cardiothoracic surgery at the Academic Medical Center (AMC) in Amsterdam (head: prof. dr. mr. dr. B.A.J.M. de Mol), and since February 2009 at the Erasmus Medical Center in Rotterdam (head: prof. dr. A.J.J.C. Bogers).





Appendix IV

List of publications



List of publications

de Lind van Wijngaarden RAF. Apoptose en activatie van neutrofiele granulocyten in ANCA-geassocieerde vasculitis. *Ned Tijdschr Geneesk* 2002;5:25-6.

de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, Noel LH, Ferrario F, Waldherr R, Hagen EC, Bruijn JA, Bajema IM. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 2006 Aug;17(8):2264-74.

de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, Noel LH, Ferrario F, Waldherr R, Bruijn JA, Bajema IM, Hagen EC; EUVAS. Chances of renal recovery for dialysis-dependent ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 2007 Jul;18(7):2189-97.

Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage CO, Sinico RA, Stegeman CA, Westman KW, van der Woude FJ, de Lind van Wijngaarden RA, Pusey CD; European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007 Jul;18(7):2180-8.

de Lind van Wijngaarden RA, van Rijn L, Hagen EC, Watts RA, Gregorini G, Cohen Tervaert JW, Mahr AD, Niles JL, de Heer E, Bruijn JA, Bajema IM. Hypotheses on the etiology of ANCA-associated vasculitis: the cause is hidden, but the result is known. *C J Am Soc Nephrol* 2008 Jan;3(1):237-52.

Presentations

Intra-curriculaire uitwisseling tussen Leiden en Stockholm. Presented at the Medical Education Congress 2002 of the Dutch Association for Medical Education (NVMO).

Fibrinoid necrosis in ANCA-associated glomerulonephritis: A possible role for Granzyme B. *J Am Soc Nephrol* 14: 413A, 2003 and *Nieuwsbrief Ned Fed*



List of publications

voor *Nefrologie* 7(1): 105, 2004. Presented at the *American Society of Nephrology Renal Week 2003* in San Diego, CA and at the *Nefrologiedagen 2004* and *Pathologendagen 2004*.

Determinants of outcome in ANCA-associated vasculitis: *A prospective clinico-histopathological analysis*. Presented at the *European Congress of Rheumatology EULAR 2004* in Berlin.

Determinants of outcome in ANCA-associated vasculitis: a prospective clinico-histopathological analysis of 65 patients. *J Am Soc Nephrol* 15:340A, 2004 and *Nieuwsbrief Ned Fed voor Nefrologie* 7(3): 22-23, 2004. Presented at the *American Society of Nephrology Renal Week 2004* in St. Louis, MO, and at the *Nefrologiedagen 2004*.

Predictors of outcome in ANCA-associated vasculitis with severe renal involvement: a prospective clinico-histopathological analysis of 100 patients. *Kidney Blood Press Res* 2005;28:178. Presented at the *XI Vasculitis and ANCA workshop 2005* in Heidelberg.

Chances of renal recovery for dialysis-dependent ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 16: 2005. Presented at the *American Society of Nephrology Renal Week 2005* in Philadelphia, PA.

Pathology review of ANCA-associated vasculitis. Presented at the *European Congress of Rheumatology EULAR 2006* in Amsterdam.

De co-assistent beoordeeld: 'Het is wit, loopt in de weg, maar haalt wel op tijd koffie: geslaagd!'. Presented at the *Medical Education Congress 2006* of the Dutch Association for Medical Education (NVMO).

Translation of renal histology into clinical severity of ANCA-associated vasculitis. *Clin Exp Rheumatol* 2007; 25(1): S94 and *J Am Soc Nephrol* 17: 2006. Presented at the *XII International Vasculitis and ANCA workshop 2007* in Cancun, MX and at the *American Society of Nephrology Renal Week 2006* in San Diego, CA.



Appendices

Clinical and histological determinants of long-term outcome in ANCA-associated glomerulonephritis. *Clin Exp Rheumatol* 2007; 25(1): S115 and *J Am Soc Nephrol* 17: 2006. Presented at the *XII International Vasculitis and ANCA workshop* 2007 in Cancun, MX and at the *American Society of Nephrology Renal Week 2006* in San Diego, CA.

ENT-involvement is related to better renal function in patients with ANCA-associated vasculitis. *J Am Soc Nephrol* 19: 2008. Presented at the *American Society of Nephrology Renal Week 2008* in Philadelphia, PA.

Awards

'Excellent Student Award' scholarship, Leiden University Medical Center, 2002

Dr. Conrad Pirani Award, Renal Pathology Society, 2006







Keep Ithaka always in your mind.
Arriving there is what you're destined for.
But don't hurry the journey at all.
Better if it lasts for years,
so you're old by the time you reach the island,
wealthy with all you've gained on the way,
not expecting Ithaka to make you rich.
Ithaka gave you the marvelous journey.
Without her you wouldn't have set out.
She has nothing left to give you now.

And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
you'll have understood by then what these Ithakas mean.
K.P. Kavafis



