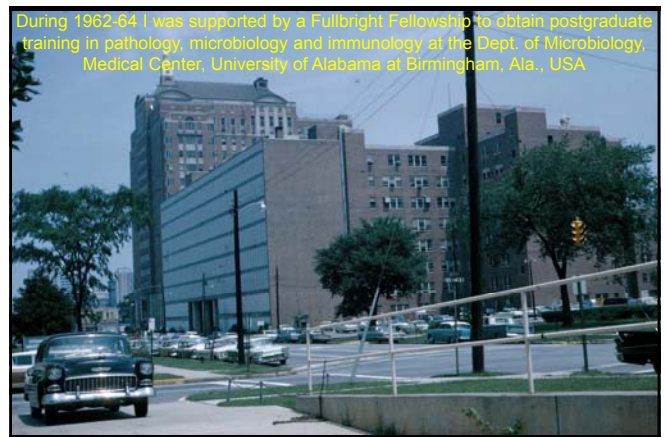


NSI Annual Meeting 2014

The advent of immunological research in Norway and NSI as a catalyst

Per Brandtzaeg
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Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), CIR, University of Oslo; and Department of Pathology, Oslo University Hospital Rikshospitalet, Norway



My supervisor was Frederick W. Kraus

Kraus & Sirisinha: Gamma globulin in saliva. *Arch. Oral. Biol.* 1962; 7: 221-33

Kraus & Konno: Antibodies in saliva. *Ann. N.Y. Acad. Sci.* 1963; 106: 311-29

I returned to Oslo with a UiO fellowship to "The House of Horror" (the Old Pathology Building from 1876) in 1964

Drawing («Black Vultures» or «Gribbene») by Ragnhild Danielsen, Secretary to Prof. Olav Torgersen

Prof. Olav Torgersen

Professor Olav Torgersen (1907-1978):

Searchlight on pathology

In contrast to earlier days' misunderstanding of pathology as a «dead» science concerned mainly with descriptive morphology, modern pathology even more than before aims at correlating function with structure of cells and tissues - -

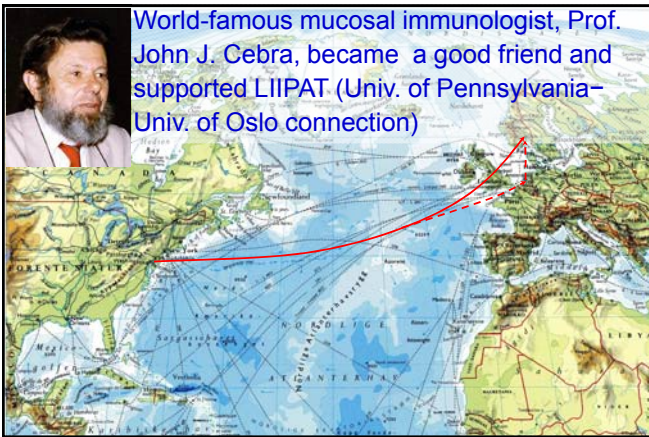
Tidsskr. Nor. Lægeforen. 82: 224, 1962

The Old Pathology Building, Rikshospitalet (1876-1970)

The beginning of the first Norwegian laboratory fully devoted to immunology and immunopathology, LIIPAT, which Torgersen wanted me to develop

Opening of LIIPAT, spring 1965

Prof. Torgersen, leader of the Norwegian Cancer Society



World-famous mucosal immunologist, Prof. John J. Cebra, became a good friend and supported LIIPAT (Univ. of Pennsylvania–Univ. of Oslo connection)

John's connections with LIIPAT

- 1994: John is a guest lecturer at Rikshospitalet, Oslo
- 1995: John obtains a fellowship from the Research Council of Norway to spend 3 months as a Visiting Scientist at LIIPAT



LIIPAT seminar 1995



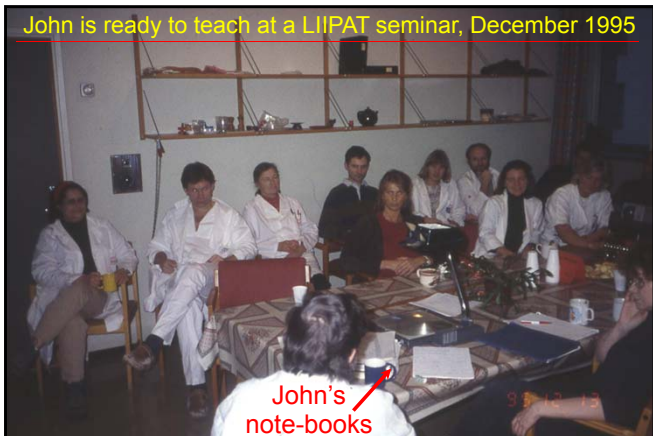
John

Ethel

- 1998: John is elected member of the Norwegian Academy of Sciences



Celebrating LIIPAT's 30th Annerevry at Bae farm, September 1995



John is ready to teach at a LIIPAT seminar, December 1995

John's note-books

The beginning of John's impact on LIIPAT's development

- 1965: John's seminal paper on fluorescent antibody conjugates
John J. Cebra & Gerald Goldstein: Chromatographic purification of tetramethyl-rhodamine-immune globulin conjugates and their use in the cellular localization of rabbit gamma-globulin polypeptide chains. *J. Immunol.* 1965; 95: 230-45
- Per met Gerald in 1965, and invited him to Oslo
- Gerald visited LIIPAT in April 1966, on his way from Stockholm
- Gerald taught Per how to purify and characterize fluorescein (FITC) and rhodamine (TRITC) fluorochrome conjugates by chromatography



Prof. G. Goldstein
Dept. of Microbiology,
Univ. of Virginia, USA

A lot of time was spent to purify fluorescent antibody conjugates

- **Brandtzaeg P:** Conjugates of immunoglobulin G with different fluorochromes. I. Characterization by anionic-exchange chromatography. *Scand. J. Immunol.* 2: 273-290, 1973
- **Brandtzaeg P:** Conjugates of immunoglobulin G with different fluorochromes. II. Specific and non-specific binding properties. *Scand. J. Immunol.* 2: 333-348, 1973
- **Brandtzaeg P:** Rhodamine conjugates: specific and non-specific binding properties in immunohistochemistry. *Ann. N.Y. Acad. Sci.* 254: 35-54, 1975



Fluorescent IgG prepared from rabbit antiserum detected human antibody-producing cells, but the old glass filters provided indistinct colour signals (LIIPAT, 1966)

IgA (fluorescein) IgG (rhodamine)

But praise the Dutch, LIIPAT was provided with the first prototypes of the "Ploemopak 1" (1969, 1971) and "Ploemopak 2" (1972) employing incident excitation light and narrow band (30-nm) interference filters

IgA- and IgG-producing cells in human gut mucosa

IgA IgG Merge

Crohn's disease

Brandtzaeg P. Mucosal and glandular distribution of immunoglobulin components. Immunohistochemistry with a cold ethanol-fixation technique. *Immunology* 1974; 26: 1101-14

The first publication based on colour separation with a Ploem-type fluorescence epi-illuminator

The paper was initially rejected because the referee wanted "... the addition of ultraviolet excitation with a colourless barrier filter to ... have enhanced histological discrimination", and concluded that "The fluorescence microscopy employed is a limiting technical feature of the study".

Brandtzaeg P. The increasing power of immunohistochemistry and immunocytochemistry. *J. Immunol. Methods* 1998; 216: 49-67 (25th Anniversary Issue)

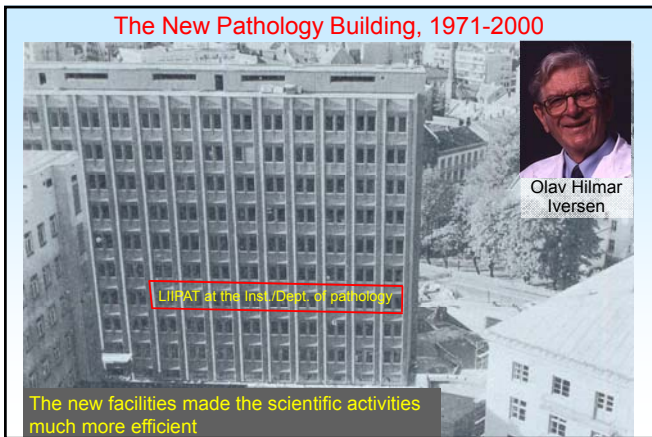
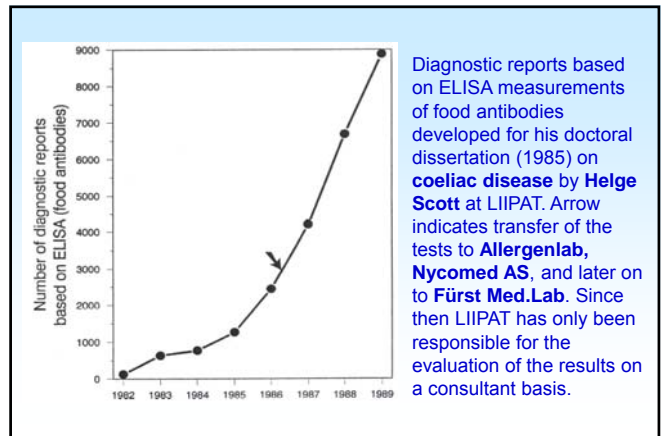
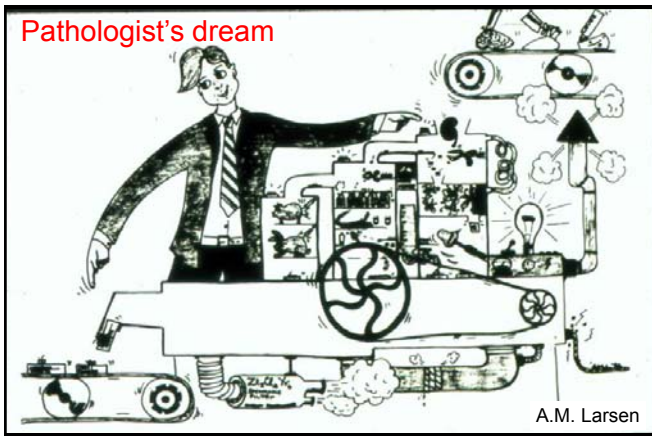
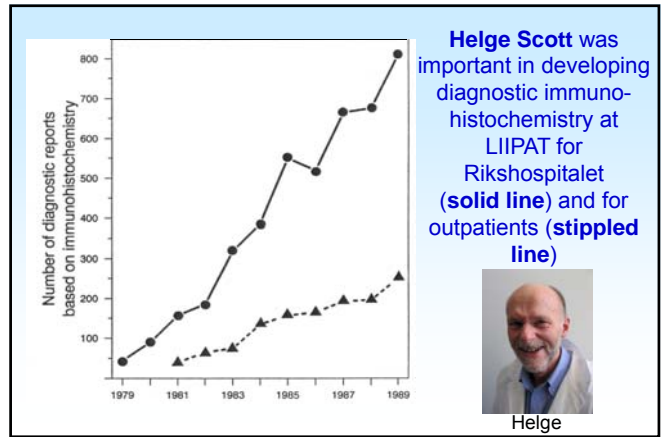
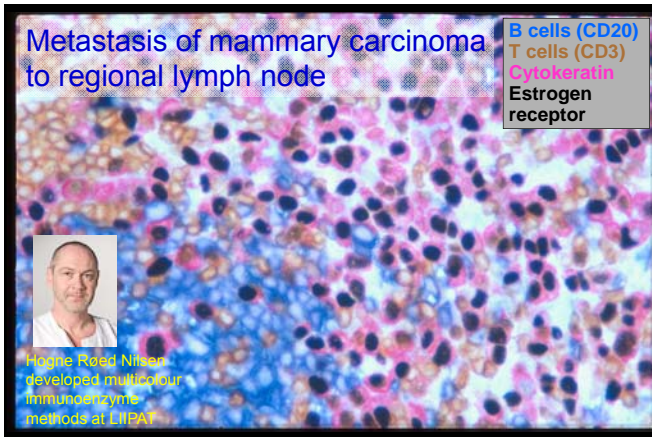
A great moment in my life: featuring James Bond and Wenche Myhre, together with Per's double immunofluorescence

Colours disclose cancer!

Aftenposten 26 June, 1985

Gut mucosa (IELs) CD3 CD4/8 CD45RB

Trond S. Halstensen developed triple immunofluorescence at LIIPAT in 1989



Medisin og helse European MRC network at LIIPAT (1991-1996)

Nyhetsbrev nr. 4 - juli 1994

Medisinsk klinisk forskning
Ny periode for det norske nettverket

European Medical Research Councils (EMRC), den medisinske avdelingen av ESF (European Scientific Foundation), har sattset på internasjonale nettverk innenfor medisinisk klinisk forskning. Sels hovedemner ble plukket ut i 1991, hvor Medisin og helse (MH) fikk ansvaret for det ene, gastroenterologisk immunologi. Nettverkene er nå vurdert, og EMRC har vedtatt at tre av de opprinnelige sels går videre. Deriblant det norske, hvor professor Per Brandtzang er leder - og en meget viktig pådriver.

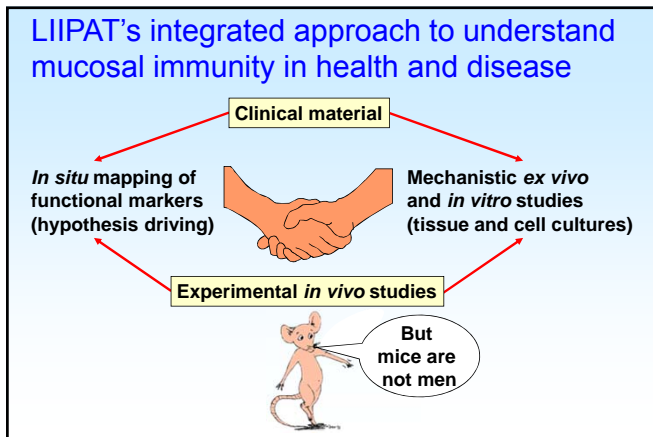
I løpet av denne 3-årsperioden har «det norske» nettverket innledet en praktisk samarbeid med European Society for Pediatric Gastroenterology and Nutrition (ESPGAN). Nettverket har dessuten inne soknald til EU om medier til å gjennomføre en internasjonal utprøving av serologiske tester for cøliaki. Videre er det startet et praktisk samarbeid mellom flere grupper som deltar i nettverket. Som følge av «workshop»-ene har professor Erik Theorelys laboratorier for transplantasjonsimmunologi, ved Rikshospitalet, innledet et praktisk forsknings-samarbeid med én gruppe i London og én i København. Ved Brandtzangs laboratorier, ved Institut for patologi på Rikshospitalet, er det startet samarbeid med én forskningsgruppe i London og én i Lübeck.

Med professor Per Brandtzang i spiss...

workshops, det såkalte «May meeting» i Oslo. Kliniske, kliniske forsøk og basalforskning har vært opp fra samarbeid av Europa, og det har foregått en meget livlig teoretisk menings- og informasjonsutveksling både under og etter samlingene. Men deltakerantallet må begrenses på en workshop, det er derfor blitt en håndplukket gjeng med maksimal interesse for de to samlinger som er satt opp for hver gang.

«Denne serie workshop»-en var kanskje den mest populære av de tre. Det var i tillegg stor entusiasme i forbindelse med foretøkk på en mulig fortsettelse av dette samarbeidet til nå har det blitt Brandtzang. Han legger til at nettverket har vært en suksess, som har bidratt til å knytte talrike bånd innenfor gastroenterologisk immunologi i Europa, og dermed fremmet internasjonalt samarbeid mellom forskere.

Medisin og helse er en avlagret avsnitt, som skildrer til åpne meninger.



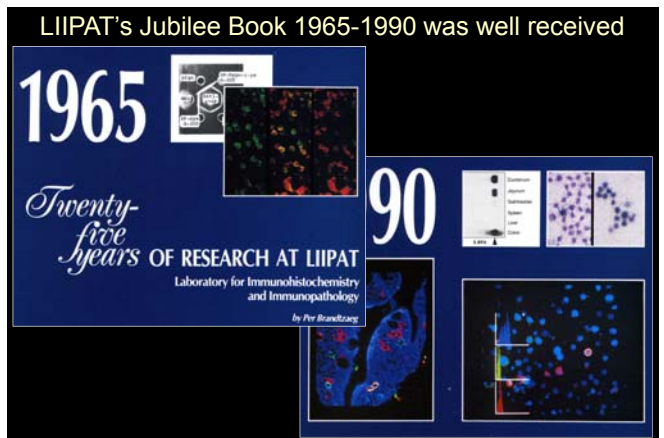
Several PhD students from LIIPAT have obtained important leading immuno-clinical positions in Norwegian medicine (3 examples)

- **Dag Kvale:** Human Secretory Component. Cellular Studies and Clinical Applications for Patients with Cancer and Liver Disease. *Dr. Med., Univ. of Oslo, 1989.* (ISBN 82-90187-47-5).
- **Richard W. Olausson:** Cytokines in Coeliac Disease: An Epithelial Perspective. Focusing on interferon-gamma, interleukin-15, and chemokine receptor 9. *Dr. Med./Ph.D., Univ. of Oslo, 2006* (ISBN 82-8072-676-4, No. 409).
- **Inge Dale:** The Human Leucocyte L1 Protein (Calprotectin): Purification, Characterization, and Distribution Analyses in Blood and Tissues. Oslo. *Dr. Med., Univ. of Oslo, 1991.* (ISBN 82-90252-37-4). In cooperation with the Dept. of Immunol. and Blood Bank, Ullevål Hospital.

Calprotectin is a heterodimer of S100A8 and S100A9 subunits (also known as L1 heavy and light chain, Mrp8/14, calgranulin A/B, and cystic fibrosis antigen)
 CALPRO AS (Arnstein Arnebergs vei 30, 1366 Lysaker)
 E-mail: mail@calpro.no

Gaddy JA et al. The host protein calprotectin modulates the *Helicobacter pylori* cag type IV secretion system via zinc sequestration. *PLoS Pathog.* 2014; 10: e1004450

Prof., Infection Med. Dept., Ullevål Univ. Hosp., OUS
 Head, Oslo Blood Bank, OUS
 Chief Med. Officer, CALPRO



The LIIPAT mucosal immunology group 2005

Section 1 – SIB Secretory immunity and B cells Finn-Eirik Johansen	Section 2 – VEC Vascular endothelial cells Guttorm Haraldsen	Section 3 – IRA Immune regulation and allergy Frode L. Jahnsen	Section 4 – GID Gastrointestinal diseases Per Brandtzaeg
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There is a need for a simple non-invasive readout as a proxy for intestinal induction of secretory immunity in field trials of oral vaccine

Brandtzaeg P. Do salivary antibodies reliably reflect both mucosal and systemic immunity? *Ann NY Acad Sci.* 2007;1098: 288-311

RESEARCH ARTICLE Open Access
BMC Infectious Diseases 2014; 14: 482

Experimental infection of healthy volunteers with enterotoxigenic *Escherichia coli* wild-type strain TW10598 in a hospital ward

Steinar Skrede^{1,2}, Hans Steinsland^{1,4}, Halvor Sommerfelt^{1,5}, Audun Aase⁵, Per Brandtzaeg^{6,7}, Nina Langeland^{1,2}, Rebecca J Cox^{2,8}, Marianne Sævik¹, Marita Wallevik¹, Dag Harald Skutlaberg⁹, Marit Gjerde Tellevik¹⁰, David A Sack¹¹, James P Nataro¹² and Anne Berit Guttormsen^{13,14}

1-5, 8-10: Haukeland University Hospital, Bergen
 5-7: LIIPAT, UiO/CEVI, and Norwegian Institute of Public Health (NIPH), Oslo

Aase A ... Brandtzaeg P: Salivary IgA as a non-invasive readout for intestinal immune response against experimental enterotoxigenic *Escherichia coli* (ETEC) infection. *Submitted, 2014.*

Senior Scientist
 Audun Aase

Network Grant from the Research Council of Norway (GLOBVAC Programme 2009-11, and P.B. (2012-14):
Developing vaccines against diarrhea caused by *Escherichia coli* and *Shigella* (EntVac)

Co-directors:

- **Halvor Sommerfelt (PI)**
Center for International Health, Univ. of Bergen, Bergen; and Norwegian Institute of Public Health, Oslo
- **James (Jim) P. Nataro**
Center for Vaccine Development, Univ. of Maryland School of Medicine, Baltimore, MD



J.P. Nataro

The first new aera of **Norwegian Immunology** began when **Jacob B. Natvig** came to Oslo in 1966

- **Jacob** was cand.med. from UiO (1959) and PhD from Gade's Inst. and Broegelmann Research Lab. for Microbiology, Univ. of Bergen (1966)
- His mentor was Prof. **Olav Tønder** who in 1980 was succeeded by Prof. **Roald Matre** as Head of Broegelmann Res. Lab. and then in 1991 by Prof. **Roland Jonsson**
- After his doctoral degree about autoantibodies, Jacob went for a research stay as postdoc with the famous physician and immunologist **Henry G. Kunkel** at the Rockefeller University in New York
- Jacob was then, in 1966, offered to be the Chief Physician and Head of the **Institute of General and Rheumatological Immunology (IGRI)** – newly established as part of Rikshospitalet by generous donations to rheumatological research from the Norwegian people and initiated by the Head of the Rheumatological Hosp., Prof. **Erik Kåss**
- It was important for the development of LIIPAT that I for several years was invited to participate in the research seminars at IGRI, with the requirement that I contributed on the same terms as Jacob's scientists



Henry G. Kunkel

De tre Riker
Rikshospitalet 1826-2001

The history of immunology at Rikshospitalet (RH) is well covered in this chapter (pp. 250-260) from 2001

Immunitet – venn eller fiende?

PER BRANDTZÆG, FRODE VARTDAL OG JACOB B. NATVIG

- One of the doctoral fellows from IGRI, **Stig S. Frøland** (PhD in 1973), subsequently (from 1975) trained in clinical infection medicine at Ullevål Hosp., and was then employed at the Dept. of Internal Med., Rikshosp. (1979), for later to become prof. associated with the Section for Haematol. Disorders
- **Stig** is a prominent clinical immunologist with a profound interest in HIV/AIDS and immunodeficiencies
- **He has a special sense of humor!**

The second new aera of **Norwegian Immunology** began when we in 2000 moved into the hospital at Gaustad

- **Erik Thorsby** was first trained in surgery at Ullevål Hospital where he obtained his PhD on HLA molecules, supervised by Prof. Morten Harboe at the Inst. for Experimental Med. Res.
- When the transplantation surgeon Prof. **Audun Flatmark** was able to establish a **Tissue Typing Lab.** at Rikshospitalet in 1970, he also succeeded in employing Erik as its first Head; the lab was in 1984 attached to UiO with the name **Inst. for Transplant. Immunol. (ITI)**
- Erik transplanted a piece of skin from one colleague to another and the specimen before (left) and after (right) the rejection reaction is depicted. This generated antibodies in the recipient against an as yet unknown tissue type (HLA-B5) expressed by the donor cells
- Since 1999, ITI has been named **Inst. of Immunol. (IMMI)** after merging with IGRI, and Erik became Head of the institute
- An important «bridge» to the clinics is **Knut Lundin** who got his PhD at ITI/IMMI and then became a Senior Consultant and Lecturer at the Dept. of Med., Rikshospitalet



Prof. Erik Thorsby



Dr. Knut Lundin

Doktorskole og medisinstudium
Det medisinske fakultet ved Universitetet i Oslo gjennom 200 år (1814-2014)

This book from 2014 covers the development of the Medical Faculty, UiO, during the last 200 years

IR
Center for Immunology Research

Ludvig M. Sollid was a joint research fellow at LIIPAT and ITI, and got his PhD on coeliac disease in 1992

Øivind Larsen

- It also gives a description of the history of the **Excellence Initiative (SFF)** announced by the Norwegian Research Council in 2001, and the development of **CIR** (established in 2007), headed by Prof. **Ludvig M. Sollid** at IMMI
- **Citation from Ø. Larsen:** Senter for immunregulering (CIR) springer ut fra sterke immunologimiljøer ved UiO og Rikshospitalet. Fra 2010 er CIR også et «Federation of Clinical Immunology Societies (FOCIS) centre of excellence. CIR består av fem forskningsgrupper og blir ledet av Prof. Ludvig M. Sollid (www.med.uio.no)
- **Citation from Ø. Larsen:** Nettverket «Centre for Vaccinology and Immunotherapy (CEVI), et tematisk forskningsområde ved Det medisinske fakultet, etablert i 2001 og var finalist ved utlysningen av første generasjons SFF-er (2002), ledet av professor Per Brandtzæg, er en forløper til CIR».

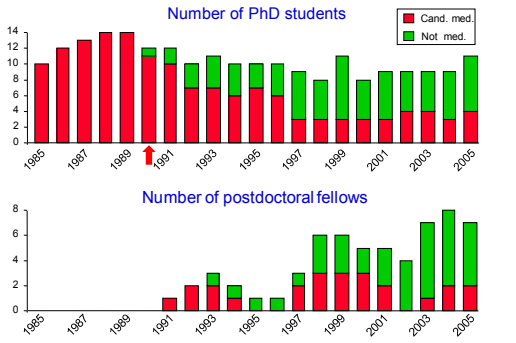
New leader and professor at IGRI from 1983

- When **Jacob B. Natvig** became the **Director of Rikshospitalet (1978)**, Prof. **Morten Harboe** moved with his immunological research group at Ullevål Hosp., UiO, where he had been for 20 years, to become the **Head of IGRI in 1983**
- Morten had received the first «immunological doctoral degree» in Norway (1961) on the genetics of immunoglobulins at the Inst. of Forensic Med., Rikshospitalet, and continued his work with Kunkel at Rockefeller Institute (1961-62)
- After Jacob resigned as a Director of Rikshospitalet (1986), he returned to IGRI as prof. of immunology and continued with an active research group, while Morten was the Head of the institute until he retired (1999)
- An important bridge between IGRI (and later IMMI) and the clinics is Morten's previous res. fellow on complement, Prof. **Tom Eirik Mollnes**, who collaborates closely with clinical researchers such as Prof. **Pål Aukrust**, Head of the **Section of Clin. Immunol. and Infect. Dis.**, Dept. of Med., Rikshospitalet



Pål

Composition of research fellows at LIIPAT



substantially the salary for young hospital physicians

The Norwegian Society for Immunology (NSI) became an important catalyst for modern Norwegian immunology

- **Jacob B. Natvig** was a strong promotor of clinical immunology, both internationally as Secretary General (1977) and later President (1992) of IUIS, as well as in Norway. In 1972 he founded «**Norsk Forening for Immunologi**» to promote general immunology, to get a specialty in clinical immunology, and to obtain fees for diagnostic tests. Because this society was founded under the Norw. Med. Assoc., it excluded non-medical members from the board, which frustrated those who had an interest in immunology without being physicians
- In 1979 I was invited to give a lecture by an informal group called «**Molecular Immunology**» under the Norw. Biochemical Soc. This group was headed by **Terje Michaelsen** (NIPH) and **Tor Lea** (IGRI), both with their PhD from IGRI
- We established an Organizing Committee lead by P.B. to explore the possibility to create an NSI open for all with an interest in immunology. At that time the **Norw. Soc. for Immunol. and Immuno-haematology** was led by Dr. **Ove Mellbye** at IGRI, and in 1977 they decided to merge with Natvig's society and collaborate for the creation of NSI. **The negotiations were successful in that all scientific issues related to immunology should be the responsibility of NSI**
- NSI was formally established in 1982 with P.B. as the first President (1982-86). We attempted to have the large **Norw. Soc. for Immunol. and Immunopathol.** make an association with NSI as well, but the Head of their board, Prof. **Kjell Aas**, simply replied: «Who is going to associate with whom?»



Jacob B. Natvig



Terje M.



Tor Lea



Ove J. Mellbye



Kjell Aas

Thanks for your attention!

