

# Obstetrics and Gynecology between clinics and research

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## Summary

An evaluation of a 25-year chairmanship at the University of Nijmegen is given. The main tasks were patient care, teaching and research.

*Patient care* was influenced by new techniques later introduced into the various subdisciplines of Obstetrics and Gynecology. Evaluation of patient care was guaranteed by annual reports focussing on avoidable factors for morbidity or mortality. Furthermore the department was visited every five years by a hospital recognition committee for specialist training. There were just two juridical complaints that finally were denied.

*Clinical teaching* involved medical students, interns and residents. The changes in teaching followed an international change from one-person lectures to student study groups. Efficacy of teaching was evaluated by an inter-university comparison of study duration. Nijmegen scored high. The evaluation of teaching for residents was done by the yearly one-day participation in the American CREOG (Council Resident Examination Obstetrics and Gynecology) multiple choice examination.

The level of final positions of trained residents can also be seen as a partial result of the quality of training. Twenty out of 128 (15.6%) were nominated as professors. The Ph.D. residents were all working in major teaching hospitals.

*Research* efforts were evaluated by the number of Ph.D.'s acquired by residents. Fifty-three percent of the residents accomplished a Ph.D. thesis. This was ten times the mean of the country.

Several new techniques were introduced by the department in the Netherlands: amniotic fluid analysis, chromosomal investigations, fetal monitoring, animal studies, laparoscopy, ultrasound, radio-immuno-assay, gasanalysis of cord blood, genetic counseling, monoclonal antibodies and prolactin-agonists.

Four research lines could be considered as an international breakthrough: the silent fetal heart rate pattern, dopamine-agonists, fetal behavioural states and homocysteine metabolism associated with neural tube defects. The last "homocysteine" project was multidisciplinary and brought about most grants. The impact factor of publications doubled from 1985 till 2000 because of publications in high-ranking general-medicine journals.

It is concluded that a university chairmanship needs fertile soil in which "the genes can express themselves". Research grants can act as a fertiliser. For an international approach prerequisites are a multidisciplinary project with publication in high ranking (general medicine) journals.

This policy was created in Nijmegen, a well known University for teaching, patient care and research.

*Key words:* Mentors; Research training; Manpower.

## Introduction

The tasks of a University chairman of a clinical department are manifold. It comprises the triad of teaching students and residents, of doing routine clinical work, of having a special outpatient consultation, to share the burden of night duties and finally to stimulate research. In all of this, one expects new and original ideas to be launched nationally and internationally.

There is no such thing as a course on "how to become a professor".

When I was asked to become chairman of the Department of Obstetrics and Gynecology at the University of Nijmegen in the Netherlands, I thought that my training was sufficient to accept the job.

I already knew the medical faculty as a student and the department as an intern and resident. Because the medical faculty started in 1951 and I arrived in 1952 the atmosphere had all the aspects of pioneering. I passed my M.D. examination in 1957 and my internship in 1959. My residency training (1959 till 1964) at the academic hospital in Nijmegen was broadened by a one-year research stay in 1961 at Western Reserve University in Cleveland, Ohio. The American period was impressive especially due to the American way of life. I made many friends.

After my residency I had to fulfill my military duties and was transferred to the Department of Surgery in Utrecht for three years where I broadened my surgical skills.

In 1967 I was nominated as the head of the Department of Obstetrics and Gynecology of St. Lucas Hospital in Amsterdam, a newly built hospital. At the same time I accepted an associate professorship at the Free University in Amsterdam.

In 1972 I was called on for the chairmanship at the University of Nijmegen.

Thus my speciality training was 13 years altogether and comprised a mixture of university and non-university practice.

### **Patient care**

Patient care at the University Department comprised the ordinary work of an obstetrician-gynecologist: the out-patient department, the delivery floor, the operating theatre, the in-patients and participation in night-duties.

At the University Hospital we cared for 50,000 visits in the out-patient unit per year, around 1,500 high-risk deliveries and 1,800 gynecological operations.

The staff increased from five in 1973 to 17 gynecologists, five to seven non-gynecologists and from 0 to 20 research associates in 1998.

The difference between a University and non-University Department is the teaching load for interns and residents. This also had the advantage that the medical histories and general examinations usually were done when a staff member came for consultation.

When I came to Nijmegen in 1972 I introduced the American daily schedule of work as I had experienced in the USA. In the early morning rounds the patients seen in the past 24 hours were presented. Discussion was free and important also from a teaching point of view. Each day from 13.00 till 14.00 hours a brown bag luncheon conference was held. From 17.00-18.00 hours everybody met again in the various subspecialties. The senior staff member who was on duty that week could organise the conferences to his or her insight.

Patient care can be evaluated first by oral advertisement by patients themselves. Another parameter is the annual report. This was done by a special team each year. Each case of morbidity and/or mortality was written down together with a judgement on avoidability.

Because the department had a license to train residents a special committee of the Dutch Society for Obstetrics and Gynecology came every five years for a one-day visit. Especially patient care and patient facilities as well as the scientific output were noted. In 1990 the department also was licensed by the Royal College of Obstetricians and Gynaecologists for exchange programs between the Netherlands and the United Kingdom.

### **Teaching**

My teaching was greatly influenced by the teachers that I encountered during my medical studies. They served as good examples.

However the teaching changed due to international student movements. The student revolution started in Berkeley (California USA) and reached Paris through Tokyo. A sole teacher and a passive audience were no longer tolerated. Moreover continuous repetition in the medical curriculum was mandatory so that things were not forgotten in the successive years. Topics of choice to be studied in student groups were also asked for.

From 1969 onwards this international thrive to change the curriculum was also felt in Nijmegen. The University of Maastricht in the Netherlands was the first to radically change its teaching program. It followed the teaching program of McMaster University in Canada. The teaching became mainly multidisciplinary.

The final result of all this was the disappearance of the professor lecturing before a big audience. Demonstration of patients was limited to small groups of students. In fact the professor disappeared.

Recently the medical curriculum for students in Nijmegen was judged by a committee to be quite good.

At Nijmegen 43% of the students passed their doctoral examinations after five years and in Maastricht 41%. They were number one and two in the university ranking in the Netherlands in 2001.

The teaching of residents was evaluated once a year by participation in the one-day examination of CREOG (Council Residents Examination Obstetrics and Gynecology). Even for experienced gynecologists this examination had a very high level of quality. Not too many passed. The final goal of this examination was to see if progress had been made in comparison with previous results.

Only the candidate and the chairman knew the result. The negative results of the group were used for the regular teaching of that year after the examination.

## Research

Research is necessary to solve clinical problems. These problems usually have to be identified and solved in coöperation with the laboratory.

It is not easy to correctly evaluate the efforts of a research team. This problem can be illustrated by the various attempts in the Netherlands to structure and evaluate scientific output of universities.

Till I came to Nijmegen in 1972 a professor had all kinds of freedom. There were well equipped laboratories and personnel. When short of money the financial-economic director Jacques de Leeuw always found a solution.

In 1972 the organisation of Scientific Research in the Netherlands proposed to divide the research money in the Netherlands on the basis of "peer review" of scientific quality. This was considered as bureaucracy.

In 1974 the universities were by law obliged to install a scientific committee, composed of staff and students. There were many protests.

One year later the university of Nijmegen installed a pool-committee for research. Only a well written protocol could acquire research money.

In the eighties a system of conditional financing was introduced. Small scale projects could not be financed anymore. The university protested.

In the eighties the concept of "aggravation and concentration of tasks" was launched.. Under the guidance of the Royal Academy of Sciences for Nijmegen 12 programs were formulated out of the 33 that already existed. This thrive to bigger and bigger reached its nadir in the current concept of research schools, a megalomania par excellence.

The Departments of Obstetrics and Gynecology in the Netherlands went through all this and were as a discipline completely overruled.

I tried to counteract all this by trying to find my own grants allowing me to attract my own people. Of course any peer review was welcomed but already guaranteed by the grant provider and the scientific output.

It was clear to me that the academic custom of writing a Ph.D. thesis was still the best proof of research output. It demonstrated that the candidate could think and work by himself. After the seventies it became a prerequisite that most of the chapters were published in scientific "peer-review" journals. Finally an independent committee had to judge the final results. In the booklet an up-to-date literature review was given on the topic.

When I accepted the chairmanship in Nijmegen I was well aware of the local academic achievements. It was an advantage to have had my complete training there and also to have worked outside this unit for several years thereafter. The founding father of the Department was professor Lou Stolte (1954-1966). His talents were universally recognised. He had a laboratory background by having worked with professor S.E. de Jong at Leiden University on steroids. I had the privilege of being one of his first residents starting my training in 1960.

### *The first years of the department: 1954-1966*

New techniques for research and patient care were developed by Stolte together with Dr. Herman van Kessel, head of the new laboratory: amniotic fluid analysis, chromosomal cultures, fetal monitoring, animal studies and bio-assay of hormones.

With these techniques the department got a leading position in the Netherlands.

*Amniotic fluid analysis* was used for the prediction of Rhesus disease in the newborn. It was found that the level of bilirubin in the amniotic fluid could predict the severity of haemolytic disease in the neonate. Unfortunately this finding was only published in the Dutch literature and did not attract international attention.

*Chromosomal cultures and analysis* formed the basis for the correct diagnosis of intersex cases. The Barr body originally described in neurons was also identified in buccal and vaginal cells.

Due to this finding the Department for years was in charge of determining sex in Olympic athletes by a very simple buccal smear.

*Fetal monitoring* had started in North and South America. I was privileged in taking up this scientific and clinical topic in an early phase. The main thrive was to detect fetal asphyxia in an early phase.

*Animal studies* were needed if the answers could not be given by human studies. This was especially true for the issue of placental passage of vitamins and hormones. The placenta of rhesus monkeys was in terms of structure and function quite comparable to the human and was used for this purpose. A special monkey colony was raised.

*Hormones* could only be determined in this time period by bio-assay. The assay was used for HCG and FSH mainly.

### *The "middle" years: 1966-1972*

Stolte was succeeded by Jaap Mastboom (1966- 1982). Mastboom was trained in Amsterdam by professor van Bouwdijk-Bastiaanse. He was known as a superb clinician and surgeon.

*Laparoscopy* was introduced by the Nijmegen clinic in the Netherlands in 1968 as well as *ultrasound*.

A special issue was the reconstruction of the absent vagina. The technique was published extensively by Davidov. Later on the reconstruction of the septate uterus, reconstruction of the Fallopian tubes and of the deficient pelvic floor were added and attracted a lot of patients.

Because the elaborate technique of bio-assay of hormones could be replaced by *radio-immuno-assay* (RIA) the laboratory staff developed these techniques.

### *The "late" years: 1972-1998*

When I was appointed in Nijmegen Jaap Mastboom and I agreed to work with a rotating chairmanship. Because we were complimentary characters the work atmosphere was pleasant and efficient. Mastboom abdicated in 1982 and Rolland was appointed as professor in 1980.

Clinical research lines were continued or newly developed.

*Infertility* was an important topic. The interests ranged from animal studies (tubal and egg transport in the hamster) and ovulation in monkeys, the menstrual cycle, prolactin, the normal and abnormal menstrual cycle, endometriosis, infertility problems, the acrosome reaction, cervical mucus, and in vitro fertilisation.

Research on *early pregnancy* used ultrasonic, chromosomal, endocrine and homocysteine determinations. It could be reported that half of the spontaneous expelled products of conception had chromosomal abnormalities especially trisomic ones. Seventeen- $\alpha$ -hydroxyprogesterone was clinically inefficient in threatening abortion cases.

Women who experience a spontaneous abortion three or more times have a chance of almost 80% of having a normal pregnancy outcome thereafter. This does not imply that research on intrinsic or extrinsic causes can be avoided.

*Genetic counselling* was an important multidisciplinary activity and already carried out in the early seventies. The initiative was started by the Department of Paediatrics.

In the middle eighties *preconceptional counselling* was launched. It became more and more clear that the success of a given pregnancy can depend on preconceptional or periconceptional measures.

*Urinary incontinence* was enriched by the multichannel urodynamic measurements before operation. The recording of intra-urethral pressure could even predict incontinence to occur after a vaginal delivery.

Research on *praemature labour* was concentrated on phospholipids in the amniotic fluid and hyaline membrane disease as well as the value of uterine inhibiting drugs.

*Pathophysiology of pregnancy* centred around bloodpressure, the value of salt restriction during pregnancy and the development of pre-eclampsia.

*Prenatal diagnostics* were introduced in 1988 after debate on the (continuing) issue of abortion.

*Signal-data analysis* by computer was of value for all kinds of projects. Especially animal studies and fetal monitoring profited. But the computer also provided the clinical data for the annual report of the Department.

*Fetal monitoring* was installed in each delivery room and had to be used in all deliveries. This facilitated the morning rounds and the discussion of cases. Next to that the fetal ECG was studied and the fetal tachogram.

*Ultrasound* was introduced very early in the Netherlands. The most fascinating finding was the recognition of fetal behavioural states.

*Hyperprolactinaemia* in the nonpregnant state had to be cured by hypophysectomy. Due to the studies with prolactin-antagonists surgery was no longer necessary.

*Animal studies* were performed in chronic fetal sheep preparation. This allowed studies on hypoxia produced by various mechanisms.

*Gasanalysis of cord blood* was introduced for use in each delivery. With this technique it was possible to detect more jeopardized babies than by clinical judgement alone.

Due to the fact that HCG could only be determined by RIA in Nijmegen the department functioned as the national *mole consultation center*.

Gynaecological oncology concentrated on immunology and on *monoclonal antibodies* with the possibility of immunotargeting.

*Homocysteine* was not known in obstetrics and gynecology but turned out to be involved in the pathogenesis of neural tube defects and vasculopathy. It became an internationally known project.

Out of these projects four were first in the international literature and became well known:

- the silent fetal heart rate pattern;
- dopamine-agonists;
- fetal behaviour;
- homocysteine and neural tube defects.

This does not mean that the others are inferior but that the researchers just developed the concept first.

#### *The silent fetal heart rate pattern*

de Haan *et al.* [1] noted that in case of anencephaly or sedatives given to the mother there was no variation in the fetal heart rate pattern. This so-called silent pattern was later also recognised in fetal sleep- states, cases of fetal distress and the administration of sedatives or analgesics to the mother during pregnancy or labor. This escaped the attention of our American colleagues (Edward Hon *et al.* at the University of Southern California) because the administration of sedatives or analgetics to the mother was a normal (American) procedure during labor.

*Dopamine agonists*: prolactine is the hormone that initiates lactation. This hormone can also be secreted by adenomata of the pituitary gland outside the puerperium. Ovulation will then be suppressed and there will be a concomitant amenorrhea. This situation results in infertility. The pharmaceutical industry had developed dopaminereceptor-agonists like bromocryptine and quinagolide. These new drugs were first tested in the de Wever Hospital in Heerlen and thereafter in our unit by professor Rolland. Due to these clinical investigations the newly developed dopamine-agonists could be registered for clinical use and are now widely accepted.

#### *Fetal behavioural states*

The study of fetal behavioural states was initiated by Chester Martin Jr. and Heinz Prechtl (professor in developmental biology at the University of Groningen). They wanted to work out the idea that the behavioural states of the newborn were also existent in utero.

Bots *et al.* [2] recognised the possibility of recording fetal eye movements by ultrasound. This opened the possibility of describing rapid eye movement (REM) sleep.

Four behavioural states could be described by Nijhuis *et al.* [3]:

State 1F is quiescence, interrupted by startles. There are no eye movements and fetal heart rate (FHR) is silent.

State 2F: comprises frequent and gross body movements. Eye movements are usually present. The FHR pattern has a wider oscillation bandwidth. Frequent accelerations of FHR are associated with movements.

State 3F is characterised by the absence of gross body movements, but eye movements are continually present.

State 4F can be summarised as the “jogging fetus”. FHR shows large and long-lasting accelerations or sustained tachycardia.

State 5 is observed in the newborn as crying. This could not be heard in utero, either because this state is not present or not audible due to the amniotic fluid.

### *Homocysteine and neural tube defects (NTD)*

For birth defects a new concept was developed by Smithells *et al.* [4] underlining the importance of the preventive effect of folic acid for neural tube defects. We started research on this topic in 1983 and found that hyperhomocysteinemia rather than folic acid deficiency was the key factor for the pathogenesis of this severe birth defect. Homocysteine is an amino-acid that the body uses for the construction of proteins. Homocysteine is methylated to methionine by the transfer of the methyl group of methyltetrahydrofolate. The transfer is catalysed by the enzyme methylenetetrahydrofolate reductase (MTHFR). The so-called methylation cycle serves as methyl donor the “one-carbon-metabolism”. This metabolism is essential for the synthesis of DNA and tRNA, proteins and lipids. Folates are essential for this methyl-donor cycle. When the homocysteine concentration in the blood is elevated the effect of this sulfur-containing amino-acid is devastating for dividing cells and also for the endothelium.

Studies with rat-embryos suggested a disturbance in DNA expression due to a deficient methylation of homocysteine into methionine and therefore a lack of methyl groups.

Two genetic mutations were found in women with neural-tube offspring. These polymorphisms in the MTHFR gene are associated with a decreased activity of the enzyme and a disturbance of the methionine-homocysteine metabolism. The observed elevated homocysteine concentrations in individuals with or without genetic mutations can be lowered by synthetic folate or folate enriched food. Observations in women with offspring with other birth defects than NTD (orofacial clefts and congenital heart defects) suggest similar mechanisms to be involved.

Hyperhomocysteinemia was also found in women with recurrent abortion.

Homocysteine was recognised as an independent risk factor for vascular disease. Obstetrical confirmation of this hypothesis could be found for placental abruption and recurrent abortion.

The impact that homocysteine has on human reproduction was reviewed in this journal [5].

My valedictory lecture, held in April 1998, was attended by 1,000 persons in St. Stevens Church in Nijmegen. Almost all European countries were represented because of my function as secretary-general for eight years of the European Association of Obstetrics and Gynecology. I lectured on the topic of folic acid administration and the prevention of birth defects because it was a concise topic, the last one in my career, very successful in attracting top journals, and according to Science a multifactorial disease that had to be studied intensively.

### *Grants:*

The above-mentioned projects in total were subsidised with 7 million Euro in total mainly by the Prevention Foundation in the Netherlands. In this way these projects made themselves self-supporting and independent of all bureaucracy that was going on in the medical faculty and university in teaching and research.

### *The impact factors of publications:*

International efforts produced a valuable list of numerical values for the various scientific journals and various indices were developed like the number of citations of a report or the impact factors of articles that are present in the SCI Journal Citation Reports. When scientific publications are rather constant in a certain period the impact factors increase due to publications in more high ranking journals (Table 1). This was highly due to the homocysteine project, an outstanding project for multidisciplinary coöperation.

To avoid the problem that journals with a rather restricted number of readers (professional journals) are overruled by journals with a large number of readers the medical faculty in Nijmegen introduced the concept of quartiles of journals. Those ranking high in all kinds of professions are now equally honoured. For our department this led to a 25% contribution in the highest quartile in 1989 and 45% in 1998.

Table 1. — *The scientific output of the University Department at Nijmegen University during the years 1985 till 2000.*

Year	1985	1990	1995	1997	1998	1999	2000
Ph.D. theses	6	3	10	2	4	3	5
"Peer review" publications	70	54	78	95	84	84	83
SCI impact factors (sum)	53	41	90	137	111	101	184
Professional publications	9	6	10	18	20	5	0
Abstracts	74	46	37	63	30	35	40

*Ph.D. Theses:*

In Europe the Ph.D. thesis is as old as the oldest university. Fortunately this system has not been abandoned. It goes back to the medieval period.

Over the years the Ph.D. became a real full-time program that lasts approximately four years or more.

A special day is planned in which the candidate has one hour to defend the thesis in public. The family is also present.

From the start of the department in 1956 till the year 2001, 124 Ph.D. theses were produced. I was involved in 55 of them. Sixty-eight residents or gynecologists accomplished a Ph.D. thesis (53.1%). This is around ten times the mean of the country. Two colleagues acquired this degree cum laude.

The majority of these theses covered an obstetrical topic (68 or 54.8%) followed by endocrinology (18), oncology (12), subfertility (10), urology (5) and contraception (4).

Almost all these residents by now have positions in academic or major hospitals.

The persons that reached a professorship and worked at Nijmegen before are listed in Table 2.

*Commitments:*

It goes without saying that a position of chairman creates many of commitments. These obligations varied from invited lectures, membership of foundations, of committees, of boards, of national and international organisations and honoraries. They were too numerous to be listed.

One exception should be made for these obligations namely invitations to join the Editorial Board of scientific journals. This effort started with the German Zeitschrift für Geburtshilfe und Perinatalogie, followed by the Spanish Journal of Obstetrics and Gynecology and the Reviews in Perinatal Medicine.

Table 2. — *Appointments to professor of colleagues who worked in the Department of Obstetrics and Gynecology of the St. Radboud Hospital, Catholic University Nijmegen (NL) and/or defended their thesis under the guidance of staff members.*

Person	Year of nomination	Location
Eylard van Hall	1971	University of Leiden
Tom Eskes	1972	University Nijmegen
Juriy Wladimiroff	1973	Erasmus University Rotterdam
Peter Vooys	1976	Department of Pathology Nijmegen
Hans Stolk	1977	Free University Amsterdam
Jelte de Haan	1978	University Maastricht
Chester Martin jr	1978	University Nijmegen and Wisconsin
Rune Rolland	1979	University Nijmegen
Philip Buytaert	1980	University Antwerpen (Belgium)
Gerard Essed	1984	University Maastricht
Herman van Kessel	1970	Free University Amsterdam
Peter Kenemans	1987	Free University Amsterdam
Hans Vemer	1987	University Nijmegen
Herman van Geyn	1989	Free University Amsterdam
Hans Evers	1990	University Maastricht
Maas Jan Heineman	1996	University Groningen
Bart Fauser	1997	Erasmus University Rotterdam
Jan Nijhuis	1999	University Maastricht
René Verheyen	2000	Free University Amsterdam
Pieter van Dongen	2002	University Stellenbosch (SA)
Didi Braat	2002	University Nijmegen

In 1977 I was invited to take over the chief editorship of the European Journal of Obstetrics and Gynecology from Prof. Stolte. It was easy to accept this invitation because I was President of the Foundation of this Journal from 1972 onwards.

Thereafter invitations came from the Dutch Journal of Medicine (1977-1981), from the American Journal of Obstetrics and Gynecology (1989-1992) and the European Journal of Oncology (2000).

From all these the work as Chief Editor of the European Journal of Obstetrics and Gynecology was the most rewarding but also the most time consuming.

It might be concluded that the work in Nijmegen was challenging and rewarding to the benefit of patients, students and residents. The research contributed not only to the national but also to the international platform.

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