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SCIENTIFIC ACTIVITY & PROFESSIONAL EXPERIENCE

Kari J. Syrjänen, MD, PhD, FIAC

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Prof. Kari J. Syrjänen, MD, PhD, FIAC

1.EDUCATION and PROFESSIONAL CAREER

The applicant graduated in medicine at University of Helsinki, April 1, 1974. The doctoral (M.D., Ph.D.) Thesis was accepted by the Medical Faculty, University of Helsinki in 1975. Appointed as a Docent in Experimental Pathology by the Medical Faculty of Kuopio University in 1979, and as a Docent in Pathology in 1980, after having received the qualification of a Board-Certified Pathologist (Finnish Medical Examination Board) in 1980. Before appointed as Professor of Pathology in Kuopio University (1989), the applicant reached the competence for two other professor positions, Professor in Pathology, University of Oulu (3rd position), in 1988, and as Professor in Cancer Biology, University of Helsinki (3rd position), in 1988. Appointed as Professor of Pathology, and Chairman of the Department, University of Kuopio, in April 1, 1989. During the career in Kuopio University, served as the Vice Dean of the Medical Faculty (1991-1994), and as the Dean of the Medical Faculty (1994-1995). Received Certificate for Competence in Cytopathology and degree of F.I.A.C., from the International Acedemy of Cytology (USA) in 1993. In 1996, the applicant was ranked 1st position for Professor in Pathology, University of Oslo, Norway. Moved to Italy in April, 1999. In 2003, the applicant was ranked 1st position for Professor in Pathology, University of Copenhagen, Denmark. Returned to Finland in 2005 and appointed to the present position at the Department of Oncology & Radiotherapy, Turku University Hospital, Turku, Finland.

2.MAJOR ACADEMIC POSITIONS HELD (TEACHING, RESEARCH, TRAINING)

A full chronological list of positions (teaching, research and training) held by the applicant is given in the CV. Started the research training at the Department of Anatomy, University of Helsinki as a Junior Instructor, while still a medical student (1970-1972). Moved to the 2nd Department of Pathology, University of Helsinki, in 1972, to complete the MD (PhD) Thesis during 1972-1974, under guidance of professors L. Hjelt and H. Teir (item #1, List of Publications). Formal training for Board-certified specialist in Pathology was completed at the Department of Pathology, Jorvi Hospital, Espoo (1977-1978)(Prof. Hjelt), at the Department of Pathology, Päijät-Häme Central Hospital, Lahti (1978-1979)(Dr. K. Järvi), and at the Department of Clinical Pathology, Kuopio University Central Hospital, and at the Department of Pathology, University of Kuopio (Prof. Collan)(1979-1980). Following the Board Certification in Pathology (1980), appointed as a Senior Lecturer in Pathology for 5 years, but held the position between 1983-1985, before being appointed as the full-time Director of the Laboratory of Pathology, Finnish Cancer Society, Kuopio (1985-1987). One of the key tasks of this laboratory is to run the organized mass-screening for cervical cancer in Kuopio province. Appointed as the first Research Professor of the Finnish Cancer Institute in 1987, but held this 5-year position only for two years (1987-89), before elected as Professor of Pathology, University of Kuopio in 1989 (among 11 applicants, 1st ranking from all three international referees). Combined with the full-time professorship and Pathology Chair, the applicant hold the Chair of the Department of Clinical Pathology, Kuopio University Hospital. The applicant also continued as the part-time director of the Laboratory of Pathology, Finnish Cancer Society, in Kuopio, until the end of 1996, when the laboratory went to private ownership. Moved abroad in 1999, gained the status of Visiting Professor at the Department of Pathology, University of Siena, Italy, and subsequently (2001) moved to National Health Institute (ISS), Rome, Italy, to coordinate a

multi-centre HPV-HIV research project (DIANAIDS 2) in Italy. In January 2005, accepted a position at the Department of Oncology & Radiotherapy, Turku University Hospital, Finland. As a senior scientist, the applicant currently co-ordinates a group of active young post-doc fellows conducting research in different fields of clinical oncology. Meanwhile, the applicant continues co-ordinating the multinational screening project in Latin America (the LAMS study) and another multi-center project in Italy (HPV-PathogenISS project), of which a new report appears at the moment (October 2006) almost once a month.

3.RESEARCH EXPERIENCE

3.1.Domestic Research Projects

Production of the scientific communications started at the Department of Pathology, University of Helsinki, with the completion of the M.D. Thesis, published in 1975 (item #1). After military service (1975-1976), the research continued since 1977, in Jorvi Hospital, Espoo. As a result of the research activity during the 29-year time span in Finland and abroad, a total of 678 original publications (monographs, reviews, book chapters), and 451 congress abstracts (and other scientific communications) have been produced (1975-2006.)

3.1.1.Tumor-host relationships and experimental immunology research

During 1972-1978, the main interest of the research was focused on lymph nodes and their reactions to human and experimental cancer. This work (also including experimental animal research) continued (although with gradually declining intensity) until the early 1980's, and culminated in the writing of a monograph: The Lymph Nodes. Reactions to Experiment and Human Tumors, published in 1982, including a comprehensive review of the work done by that time (item # 68). These studies are closely linked with the experimental immunology studies in the early 1980.s in Kuopio, assessing some of the basic mechanisms of T-cell re-circulation and T-B cell interactions, using the chicken bursa model. This led to first evidence on the role of chicken bursa as a peripheral lymphatic organ with definite T-cell compartment as well.

3.1.2.Papillomavirus research

The applicant became interested in genital Human papillomavirus (HPV) lesions already in February 1977 (while in Jorvi Hospital), following the primary reports on their newly recognized association with cervical cancer precursors few weeks earlier. The frequent association of HPV lesions with all grades of cervical precancer lesions became evident immediately. These early observations formed the starting point to the applicant.s interest in papillomaviruses, which has continued 25 years by now, and being focused on HPV lesions not only in the genital tract, but also on those found in upper aeordigestive tract.

These early papers from the late 1970's and early 1980's (with important pioneering reports) together with the two subsequent Papillomavirus Textbooks (1987 and 2000) and large number of communications from the Kuopio Cohort Study (1981-1998), have created the basis of the applicant.s **worldwide recognition** as one of the pioneers in HPV research. This is evidenced by the progressively growing number of invited reviews, editorials and book chapters, as well as invited presentations in international congresses, far exceeding 210 at present.

Since 1981, the applicant established an internationally recognized Papillomavirus research group in Kuopio. The major achievement by which this group is best known

worldwide, is the set-up and continuation of a unique long-term prospective follow-up (cohort) study for HPV-infected women for 18 years (1981-1998). Kuopio PAPILLOMAVIRUS PROJECT was the first prospective cohort study in the world, when started in October 1981 and continued to be the only one of its kind until the early 1990.s. Apart from the published almost 400 papers, the major achievements of the PAPILLOMAVIRUS PROJECT include 20 Doctoral Thesis, and organization of the most important annual Papillomavirus conference (the 1985 International Papilloma Virus Workshop) in Kuopio. Since its onset, the project received support e.g. from NIH/NCI (USA)(1985-1987), and its results have been presented as invited lectures in congresses throughout the world.

The data accumulated from papillomavirus research by the mid 1980's were summarized in the 16 chapters (contributed by prominent international experts) of the first ever published HPV textbook entitled: Papillomaviruses and Human Disease, edited by K. Syrjänen, L. Gissmann & L.G. Koss (Springer Verlag, 1987, item #338). As a tribute to our project, discontinued in Kuopio 1999, the second textbook: Papillomavirus Infections in Human Pathology (615 pages, 21 Chapters) was authored together with Prof. Stina Syrjänen (Wiley & Sons, 2000), being the most comprehensive source of information available on HPV-associated human pathology today. Since 1993, a part of Kuopio Papillomavirus Group moved to Turku University, where the work was continued with Prof. Stina Syrjänen as the head. Collaboration between the Kuopio and Turku groups was intense and beneficial to the Project, while capable of utilizing the facilities of two Universities. Results of this collaboration are found in the list of papers (items from #400 onwards).

3.1.3.Breast cancer studies

Although best recognized by his contributions in papillomavirus research, the applicant has maintained the old interest in another major focus of the present-day cancer research, i.e., breast cancer, particularly its biological prognostic factors. This interest was revived more recently, when Kuopio Cancer Research Centre (KCRC) was established in 1988 and the applicant was elected as the Chairman of the Board and Scientific Director. In 1991, KCRC designed and started another major prospective cohort study focused on breast cancer patients, known as KUOPIO BREAST CANCER STUDY. In few years, over 500 women with breast cancer, 1.000 women with benign breast tumors, and additional 700 age-matched healthy (population) controls, were enrolled in this major project, headed by the applicant until 1996. By the late 1990.s a substantial number (60-70 items) of original reports (and two doctoral thesis) have been published from this project, many of which in prestigious international cancer and pathology journals (List of Papers).

3.2.International Research Projects

Apart from being the designer and coordinator of the above two major domestic research projects, the applicant has gained widely recognized experience as an initiator, designer and coordinator of a number of multi-national research projects funded by European Commission (EC) and, most recently, by Italian Health Ministry. Since the 1994, the applicant has had an uninterrupted funding from the EC, extending until 2006.

3.2.1.HPV and oesophageal cancer

The first of these multinational projects (Contract # TS3* CT94-0295) was part of the STD3 Programme, covering the period 1994-1997. In this project, the researchers working in

three EC-countries (Germany, Finland, Italy) got access to a unique material of over 2.000 tissue biopsies collected from 700 patients with oesophageal cancer in the high-incidence area of Henan Province, North China. Oesophageal cancer is another human malignancy, suggested to be associated with HPV by the applicant in his pioneering studies in 1982, and subsequently studied for this evidence by several other groups (data summarized in the special chapter of the new Textbook). This Oesophageal Cancer Project was officially terminated in 1997, but the outflow of scientific reports continue until now (some are still in print and one under preparation). The milestone report of this project was the single largest series (>700 cases) of oesophageal carcinomas ever analysed for HPV, providing conclusive evidence on the association of this tumour virus in oesophageal squamous cell cancer, at least in the high-risk areas of this disease.

3.2.2.Cervical cancer screening in NIS countries

The second and still ongoing EC-funded project (Contract # ERB IC15-CT98-0321) was designed and initiated by the applicant as the coordinator while still in Kuopio, but at transition abroad in 1999, was transferred to Turku University (coordinated by prof. S.Syrjänen). This project belongs to the INCO-COPERNICUS Programme of EC, and is known as the NIS/CCE Cohort Study, continuing until the first quarter of 2002. This study is participated by 9 research groups from two EC countries (Finland and Italy) and those from three NIS/CCE countries (Russia, Belarus and Latvia), with the main focus being in the testing of different optional diagnostic tests (PAP smear, PCR and Hybrid Capture II) as screening tools of cervical cancer in these low-resource settings. Based on the excellent results of the organised mass-screening programme in Finland, and on the know-how of the coordinator (having run this programme in East-Finland for 16 years), this multi-national project is testing the performance of three optional diagnostic tools in early detection of cervical cancer precursors. The long-term aim is to use this information as the basis for selecting the cost-effective strategies for cervical cancer prevention in these three NIS countries with high-incidence but limited resources for preventing this disease. This combined cross-sectional and cohort study is based on meticulous examination and prospective follow-up of **3.187 women**, representing patients in three categories of risk for cervical HPV infections and cancer. Due to the prospective nature of this study, the main publication activity started after termination of the follow-up, to enable the full exploitation of the uni- and multivariate survival analyses. **At present (late 2006), this project is an active phase of reporting, already resulted in a sizable series of recent papers.**

3.2.3.Cervical cancer screening strategies in Latin America

The third, and the most recently started EC-project (Contract # ICA4-CT-2001-10013) is funded by the INCO-DEV Programme and covers the period 2001-2004. This extensive project is participated by 8 research groups from two EC countries (Finland, Italy), from one Associated State (Slovenia), and from two Latin American countries (Brazil and Argentina). The official title of the project is: IMPROVING HEALTH SYSTEMS TOWARDS EQUALITY-BASED CONTROL OF CERVICAL CANCER IN LATIN AMERICA. Comparing PAP Smear Cytology, Aided Visual Inspection, Cervicography and Human Papillomavirus (HPV) Testing as Optional Screening Tools in Brazil and Argentina (**the LAMS Study**). The objective is to elaborate the research data needed to design a cost-effective strategy for cervical cancer screening in Brazil and Argentina, by using a combined cross-sectional (n=12.000) and cohort (n=1.000) study of women examined in four different clinics for the prevalence, pathogenesis and natural history of CIN and HPV infections. The performance characteristics (sensitivity, specificity, negative- and positive predictive value,

as well as ROC = receiver operating characteristics) of the traditional diagnostic tools (PAP smear cytology, colposcopy) are compared with those of the HPV detection methods (Hybrid Capture II and PCR) and those of the suggested screening tools for low-resource-settings (aided visual inspection, cervicography and self-sampling for HPV) in detecting significant cervical pathology (high-grade CIN lesions and cervical cancer). The long-term objective of this project is to acquire the necessary data for the basis of designing a sustainable and cost-effective strategy for an organised cervical cancer prevention programme in Brazil and Argentina.

This 3-year project is scheduled to proceed a) by establishing the magnitude of cervical cancer and its precursors as a health problem (i.e., prevalence) in target populations at different risk, b) to testing of the performance (sensitivity, specificity, PPV, NPV, ROC) of these optional diagnostic tools, and c) ending up with the synthesis of these data with a feasibility analysis and guidelines, how to improve the health systems by creating a cost-effective strategy for an equality-based cervical cancer control in these two LAM countries. **At present, also the LAMS study is a phase of active reporting, already resulted in a series of high-impact recent papers. With the conclusion f the follow-up, important new data are obtainable making possible to confirm or refute the research hypothesis. At present, a series of almost 20 new reports has been designed and several are in pipeline, contributed by all the research partners in this multi-national study. We anticipate to conclude this series of reporting by the end of 2007.**

3.2.4.HPV infections in HIV-infected women

Another ongoing project, funded by the Italian Ministry of Health, was started in Italy in 2002. This multi-centre research project (coordinated at the National Health Institute, ISS, Rome), known as **HPV-PathogenISS Project**, was designed by the applicant, who is officially the scientific coordinator of the project working at ISS. Based on several well defined multi-elemental hypothesis, the major focus will be 1) in assessment of the differences in the prevalence of genital HPV infections, CIN and cervical cancer in immunocompromised and immunocompetent women; 2) in disclosing the risk factors responsible for the different predisposition to HPV infections and CIN in HIV + and HIV- women; 3) in elucidating, by prospective follow-up, a) the differences in the biological behavior of HPV infections and their induced CIN lesions, and b) to assess the biological mechanisms behind these differences; 4) to evaluate the risk for imminent development of invasive cancer by close monitoring of the lesions progressing to CIN III; and 5) in analyzing the prognostic factors in HIV-negative and HIV-positive women progressed to invasive cancer, in a retrospective series.

The strength of **HPV-PathogenISS Project** is in its design, where most eminent research centres in different parts of Italy are contributing the patients (HIV + and HIV-, infected by HPV) into the prospective cohort, which is combined with the meticulous molecular biological analysis of similar samples collected from a retrospective series of women with all grades of CIN and also cervical cancer. The general long-term objective of this joint research project is to increase our understanding of the basic mechanisms regulating the biological behavior of cervical HPV infections and their associated cancer precursors in both HIV-negative and HIV-positive women. These data will have important implications in designing new strategies of early detection, accurate diagnosis and effective treatment of these patients, to be implemented as a part of an organized cervical cancer prevention policy in this country.

During 2005-2006, a series of 12 papers have been completed, most already published and the rest being in press in different international journals. These 12 papers form a homogeneous series of studies, where 13 different biomarkers were analyzed in a carefully characterized series of 300 CIN lesions and cervical cancer. As the final step, all 13 biomarkers are analysed by meticulous multivariate modelling. Apart from getting new insights in the molecular pathogenesis of HPV-associated cervical carcinogenesis, we anticipate to disclose 1) individual markers, 2) a panel of markers, or 3) an expression profile of any such marker panel that would have positive predictive value (PPV) high enough to make it suitable as a screening tool for CC.

3.3.Research Technology

Based at the Department of Pathology, University of Kuopio, Papillomavirus project (1981-1998) was able to fully exploit the technical know-how, facilities and equipment to conduct research in all fields of modern pathology, including the necessary DNA technology. This laboratory was among the first few worldwide to establish in situ hybridization (ISH) technology as a daily routine in HPV project (1985, i.e. the year when published), and made a significant contribution by developing a series of well established commercial ISH kits for viral diagnosis (by Stina Syrjänen) in the late 1980.s and early 1990.s (BioHit HPV-, HSV-, CMV- and EBV kits). PCR technology was adopted as soon as the first thermocyclers became available. Supplemented by an own DNA synthesizer, made our laboratory independent in availability of synthetic oligonucleotides as well. An own laboratory for cell- and tissue culture was constructed at the Department in the early 1990.s. For many years in the late 1980.s, our laboratory was a site, where numerous (some 60) foreign scientists visited for shorter and longer periods to learn this research technology.

In 1993, part of the group moved to Turku University, receiving laboratory facilities in the MediCity Research laboratories. This exploiting of the full spectrum of molecular biological technology in two Universities, made Papillomavirus project even stronger in the 1990's. Currently, with the EC funding and establishment of the large international multi-centre research projects, contributed by several research groups from different countries within and outside Europe, the **applicant as the coordinator of these projects has access to practically unlimited patient materials (of different kind) and the research technology and instrumental facilities necessary to conduct research in the divergent fields of modern pathology.** This shift from the coordination of purely national projects in Finland to the coordinator of multinational projects, is evident also from the most recent scientific production, i.e., items from #500 onwards.

3.4.Research Funding

During its 18 years of existence, the Kuopio Papillomavirus Project was satisfactorily funded by different sources of both domestic and international origin. The most important domestic sources include: the Academy of Finland, Finnish Cancer Institute, Finnish Cancer Society, Institute of National Health Insurance(KELA). The international support to the different projects of the applicant has derived from three major sources: NIH/NCI (USA), 1985-1987: BAT & FTR (UK, Switzerland), 1990-1996; and European Union (EU): STD3 Programme, 1994-1997; INCO-COPERNICUS Programme, 1998-2001; INCO-DEV Programme, 2001-2005. The total funding of the research projects headed by the applicant between **1981-2006** currently accounts for FIM 21.5 million (**3.6 million EURO**).

4.SCIENTIFIC CONTRIBUTIONS

4.1.Volume, Impact Factors and Citations

List of publications currently includes **684 original papers**, reviews or book chapters in referred international journals, and **453 congress abstracts** or other scientific communications. While spanning over a **30-year period** (1975-2006), these **684 original contributions** represent an average of **21.9 papers per year**, i.e., more than one original paper every third week, for 31 years. Inclusion of the **451 other communications** in this calculation would result in an average of **36.4 scientific communications per year**, i.e., **3.03** communications **every month**, for 31 years. Output of this volume is possible only with an effective collaboration with several research groups.

The **mean of the impact factors** (I.F.) of the **20 highest ranking** papers currently equals to **10.847** (216.935) and that of the **25** highest ranking papers **9.806** (245.174). For comparison, the highest ranking Pathology journal, American Journal of Pathology holds IF 6.441 in the most recent ranking of the journals.

In the **official ranking of 500 most cited medical scientists in Finland**, published in 2001, the total number of citations received by the applicant in referred international journals was **6.592** (for papers published in 1975-1999). The applicant was ranking 31/500 and on the third position among the 8 Professors of Pathology in Finland, second only with a narrow marginal (few hundred citations) to the two top-ranking ones. Since then, the **number of citations** received in referred international journals has increased steadily, currently reaching **8.832** (for papers published in 1975-2005).

4.2.Short Overview on the Scientific Contributions (1975-2006)

4.2.1.Tumor-host relationships and experimental immunology

This topic is covered in part above (section 3), where the scientific content of the major research projects of the applicant are described. With few exceptions, all the 620 original papers fall within the scope of cancer research. The scope of the studies published between 1975-2004 is broad, however, covering both human malignancies and including a number of studies using an experimental tumour model (mouse mastocytoma) as well.

During the 6-7 years to follow the Doctoral Thesis in 1975, my main research interest was focused on tumour-host interactions in human and experimental tumours. This led to a series of papers during 1977-1978, where lymph node reactions to both human and experimental cancer were analysed, using morphological approaches. Of special interest was the assessment of the lymphocyte re-circulation between the blood and lymphatic tissues, leading to a formulation of a hypothesis on the important role of post-capillary venules (PCV) as regulators of this traffic. This was proposed to be mediated by lymphocyte-endothelial cell interactions (adhesion). Although subsequently refined by more sophisticated techniques, these concepts represent the basic ideas well before the era of monoclonal antibodies and recognition of adhesion molecules, which finally solved the issue. This line of research continued until the early 1980.s, and concluded in the writing of a monograph on this subject (published in 1982), being the most comprehensive review on lymph node reactions to human and experimental tumours available at that time (item#68).

This line of research still continued (with declining intensity) a few years ahead in Kuopio, where some additional studies on this subject were published (items before #100) during

the early 1980.s. There was a short period between in the middle 1980.s, when the interest in our previous experimental cancer model was revived, leading to a series of papers in collaboration with the pathologists in Siena, Italy (items # 157, 158, 170, 181, 182). This opened the way to fruitful collaboration in other fields (HPV), continuing until present. During the first half of 1980.s, I also made some contributions in experimental immunology, by assessing the functions of chicken cloacal bursa under different experimental conditions (items # 75, 76, 106, 117, 128, 129). We were among the first to demonstrate that chicken cloacal bursa, previously considered to be exclusively a B-cell lymphatic organ, also contained a distinct T-lymphocyte area with functions like any other peripheral lymphatic organ. On the basis of these works, we were invited to contribute a book chapter (# 146), summarizing the state-of-art in the field.

4.2.2.Papillomavirus research

Beyond any doubt, however, the applicant is best known internationally by his contributions in the field of Human papillomavirus (HPV) research. The applicant became interested in HPV in February 1977, following the primary reports on flat and endophytic condylomas and their suggested associations with cervical cancer (Meisels et al. and Purola et al.) published at the same month.s issue of Acta Cytologica. While being at the beginning of one's pathology curriculum, the applicant recognized the potential importance of these pioneering observations and started exploring their feasibility. It became immediately apparent that these newly described flat and inverted HPV lesions proved to be extremely common among all grades of cervical precancer lesions and also found in carcinomas. This pioneering enthusiasm led to a series of papers prepared during 1977-1979, including the first review article ever written on genital HPV infections in 1980 (#35). These early observations formed the impetus to the applicant.s subsequent interest in HPVs, which has continued over 25 years by now, and focused not only on HPV lesions in the genital tract, but also on those of the respiratory-, aerodigestive-, and urogenital tract as well as the skin.

Between 1981-1999, the applicant headed an internationally recognized Papillomavirus Research Group in Kuopio, Finland. Our major achievement is the set-up and continuation of a unique, long-term prospective cohort study for HPV-infected women for 18 years. The other important achievements of this major research group are listed in Section 3. Altogether, the HPV research activity has resulted in a series of around 400 scientific reports (abstracts not included), with a significant number of pioneering primary observations in the different fields of HPV research, as summarised in Chapter 1 of our recent Papillomavirus Textbook (item #500). Such primary reports include e.g. the paper #29 (the first published case of an invasive cervical cancer with characteristic morphological changes of HPV), #31 (the first systematic survey of CIN lesions to explore their association with HPV lesions), #32, 50, 58, (describing the morphological association of HPV with bronchial cancer, subsequently confirmed by DNA-hybridization, #179), and #59, 81, 178 (describing such an association in laryngeal carcinomas).

Furthermore, the author's group was the first to provide evidence on HPV-involvement in oral squamous cell lesions, both benign and cancer (#84, 92, 94, 98, 112, 160, 165), in oesophageal squamous cell papilloma and cancer (# 83, 85), as well as in sino-nasal papilloma and squamous cell carcinoma (#88, 183). Important is also the report in 1984, where the risk factors of genital HPV infections were reported for the first time in a case-control study (item #108) All these pioneering papers have stimulated several new lines of

HPV research, where these early works are recognised as standard references in the subsequent literature by other groups. Many of the HPV papers have included in the list of selected 20 papers, to give a balanced view on the scope of the applicant's scientific production and interests during the past 25 years.

4.2.3.Breast cancer studies

In addition to HPV research, which continues to be his main research focus, the applicant revived his old interest in the biological prognostic factors of breast cancer since 1990 (for details, see Section 3). The design of the prospective breast cancer study was a logical consequence from the success of the prospective HPV cohort study, and also because of the growing importance of breast cancer as the study subject. This multi-institutional study also provided excellent facilities to utilize modern research technology available at different departments. Under the leadership of the applicant, we completed a series of some 70 papers from this project, listed among the items from #270 onwards. In these studies, also a retrospectively collected series of over 600 breast carcinomas was analysed by different techniques of modern pathology (immunohistochemistry, DNA technology, flow cytometry, quantitative pathology). A number of these reports have appeared in the high-ranking pathology and cancer journals (e.g. J. Pathol., J Clin. Oncol.), and already received good number of citations despite their recent date of publication. Together with the previous papers on breast cancer published by the author before the Kuopio breast cancer project, these reports of the 1990's make this topic the second most important line of research of the applicant.

4.2.4.Alzheimer's disease

In the early 1990.s, our laboratory had a short but fruitful collaboration with the leading Alzheimer study group in Finland and working in Kuopio (headed by Prof. P. Riekkinen, Sr.). During this intense but short period of collaboration, the groups were able to produce a number of significant contributions published in the high-ranking Neurology journals and e.g. in the Lancet. Some of these papers represented a significant novelty at that time, including the detection of immune-complexes in the skin and circulation of Alzheimer patients, implicating a possible infectious etiology and systemic involvement of this disease (items #271, 272, 291, 300, 320, 325, 345, 474).

4.2.5.Cervical cancer screening studies

During the past few years, the HPV research of the applicant has widened its scope to the large-scale international projects, assessing the value of optional diagnostic tests (HPV testing among others) as screening tools in cervical cancer prevention on the global scale. The applicant.s expertise in cervical cancer screening is derived from his 16-year period as the officer responsible for the practical running of the organised cervical cancer screening programme in eastern Finland (on the mandate of Finnish Cancer Society). Like the HPV studies of the applicant, this focus of interest in cervical cancer screening issues has been internationally recognised by an increasing number of invited presentations in international congresses, different working groups and networks, by a number of invited reviews, editorials and book chapters (items #415, 448, 470, 484, 498, 504, 506, 514, 515, 521, 650) as well as several original papers on the subject, published as a result of international collaboration (#410, 463, 480, 492, 495, 501, 538, 542). With the setting up of the three latest projects (point 3.2.2.; 3.2.3.; 3.2.4.), **this activity has clearly received the main focus of the applicant's current scientific interest.** In parallel with the progress

of the ongoing research projects, this is the field where **major contributions** of the applicant have been done **in the recent past** and are to be expected **in the near future**.

4.2.6.Gynaecological pathology, non-HPV-related topics

Along with the new links to Europe and countries in Latin America, since the late 1990's, a sizeable amount of fruitful collaboration has been started with several groups interested in the wide scope of (non-HPV-related topics) in gynaecological pathology. This collaboration is a natural continuation of the applicant's long-term interest in gynaecological pathology, previously focused almost exclusively on HPV pathology. In addition to a few communications from the 1980.s (items #69, 164, 218, 326), the number of reports in the field of gynaecological pathology has increased substantially during the past few years (items #411, 435, 437, 442, 457, 496, 505, 508, 536, 537, 539, 543, 544, 545, 547, 548), including invited reviews and book chapters. The most notable among the recent works in this category include a concise series of reports on biology of ovarian cancer (items # 464, 479, 481, 488, 489, 494), published within a short period in some of the best-ranking cancer journals (e.g. J.Clin. Oncol., Cancer Res.).

4.2.7.Studies on other human malignancies

In addition to the long list of important papers on oesophageal cancer, which in this categorization belong into HPV research, there is a substantial number of reports on studies focused on other major human malignancies. In the subsequent, included are only the topics which a) are not HPV-related and b) of which there appear more than 5 original reports in the author.s list of publications. These other human malignancies include: prostate (items #253, 277, 292, 346, 372, 377, 378, 386, 391, 393, 396, 401, 438, 476), renal (items #7, 8, 19, 24, 374, 380, 409, 427, 469, 491), gastric (items #5, 6, 14, 60, 99, 123, 429, 434, 455, 465, 471), and bronchial cancers (items #21, 36, 45, 58, 134, 143, 179, 206). Altogether, these 43 papers represent far less than 10% of the total volume of the author's publications, but several of these represent considerable novelty in their time, are published in good pathology and cancer journals, and thus also this category of works represents a non-negligible part of the author's scientific production.

4.2.8.Other (non-cancer) topics

Apart from these major lines of research focus, among the 620 communications, there are some scattered papers on topics completely unrelated to this mainstream. Included in this category are a couple of papers on ODC (ornithine decarboxylase) studies in transgenic mice from the early 1990.s, which while published in biochemistry journals, belong among the highest ranking papers of the applicant by IFs (items #272, 335), although as such are far outside the mainstream research interests of the author. Finally, a separate mention should be made to yet another specific field of pathology, in which the applicant and his group has published a sizeable number of papers (unrelated to HPV), i.e., oral pathology. This work (including several papers on salivary gland pathology) has been conducted from the initiative of the current Chair in Oral Pathology, Turku University (Prof. Stina Syrjänen), during her stay in Kuopio, i.e., before 1993.

5.PROFESSIONAL EXPERIENCE AS CLINICAL PATHOLOGIST

5.1.Diagnostic Experience

Having completed the pathology curriculum and passed the national board examination, the applicant became a Board-Certified Pathologist in 1980. Since that time, the applicant has practiced diagnostic clinical pathology daily at two separate affiliations: 1) as the

Director of Laboratory of Pathology, Finnish Cancer Society (FCSLP) in Kuopio (1981-1996), and 2) as the Head of the Department of Clinical Pathology, Kuopio University Hospital (DCPKUH)(1989-1999). FCSLP was a diagnostic cytopathology laboratory owned by the Finnish Cancer Society, and working on a private basis. Accordingly, the laboratory serves the regional hospitals without own pathologists, health centres, and private health care providers, from a widespread area of Central and Eastern Finland. At highest, the annual number of samples examined exceeded 65.000, including 15.000 biopsies (representing all fields of surgical pathology) and 50.000 cytological samples (covering the entire field of clinical cytology). Since 1981 until 1996, the applicant viewed biopsies and cytological specimens on daily basis, with the estimated annual numbers of 3.000 biopsies and 10.000 cytological samples.

As the Head of the DCPKUH, the applicant was responsible for the development and maintenance of the diagnostic level of a Clinical Pathology Department in a University Hospital, since 1989 (a position joined to Professorship). Even long before that, however, the applicant was personally responsible for the examination of all biopsies and cytological smears taken from the women included in the prospective Kuopio Papillomavirus Cohort Study, since its onset in 1981 (see 3.1.2.). This means a substantial diagnostic workload, when over 1.000 women attend the hospital Outpatient Department at 6-month intervals for 18 years. At each visit, the patients were examined on colposcopy, PAP smears and punch biopsy (usually 2-3 each time). It can be estimated, that during these 18 years, the author has examined a minimum of 30-45.000 biopsies and some 30.000 smears exclusively related to this research project. Having passed the international board examination, the author received the degree of FIAC (Fellow of the International Academy of Cytology, IAC) and the Certificate of Competence in Cytopathology, in 1993. This is equivalent to sub-speciality in cytopathology, which does not officially exist among the medical specialities in Finland, however.

5.2.Development of Quality Assurance (QA)

In the field of diagnostic clinical pathology, the Quality Assurance (QA) issues have been recently emphasized both internationally and at national level. During the past several years, the author has been involved in and closely followed these developments in both sectors. In international forum, reference is made to item #415 (Syrjänen, K.J. Quality assurance in the cytopathology laboratories of the Finnish Cancer Society. In: Compendium on Quality Assurance, Proficiency Testing and Workload Limitations in Clinical Cytology. (eds.) George L. Wied, Catherine M. Keebler, Dorothy L. Rosenthal, Ulrich Schenck, Theresa M. Somrak, G. Peeter Vooijs. Tutorials of Cytology, Chicago, Illinois, USA. pp. 134-142, 1995), where the QA practice in the FCSLP is detailed in the first international Compendium, published by the IAC. More recently (2000), the author has created the core substance of the extensive web-sites (www.icsglobal.co.uk) of an international enterprise (International Cytopathology Services, Ltd.), the essence of their mission (the ICS-Concept) being to maintain uncompromised quality in clinical cytology. By the mid 1990's, the national criteria for QA in cytopathology laboratories were designed. Under the leadership of the author, both FCSLP and DCPKUH received among the first few laboratories in Finland the Quality Certificate of the Finnish Medical Association (February 1996), as a recognition of their high technical and QA level.

5.3.Activity in Professional Societies

Since the early 1980.s, the applicant has had a privilege to serve as an officer (Chairman, President or Board Member) of a number of both national and international professional societies, promoting the professional skills of their members (see the CV). This includes both of the two national professional societies within the discipline (pathology and cytology). In Finnish Association of Pathologists (a Sub-Section of Finnish Medical Association), the applicant was a member of the Board between 1981-1982, Vice-Chairman of the Board between 1982-1984, and Chairman of the Board for over 5 years (1984-1989). In clinical cytology, the equivalent organization is the Finnish Society of Clinical Cytology. Joined the Society in 1979, elected a member of the Board in 1982, and as President & Chairman of the Board for 10 years, 1988-1998.

The national cytology societies are affiliated with the EFCS (European Federation of Cytology Societies) and IAC (International Academy of Cytology). In IAC, the author has served in a number of committees, as detailed in the CV. As the national president, the applicant has been a Member of the Council in EFCS, between 1988-1998, and had an honour to serve as the President of the EFCS in 1990-1991. In 1998, I was appointed as Chairman of the Programme Committee, EFCS.

As a practicing pathologist, the applicant is best known as **a gynaecological pathologist**, being a member of the International Society for Gynecological Pathologists since 1986. As a recognition of my contributions, I have been invited as an **Honorary Member** of two professional societies: Italian Society for Colposcopy and Cervical Pathology (in 1986), and (in 1988) **American Society for Colposcopy and Cervical Pathology** (ASCCP)(10 honorary members only), which is a highly recognised honour among gynaecological pathologists worldwide. In **April 2006**, the applicant was rewarded by **EUROGIN** (European Research Organisatio on Gynecological Infections and Neoplasia) a **Distinguished Service Award** in their tri-annual congress in Paris.

6.EXPERIENCE IN ADMINISTRATION AND LEADERSHIP

6.1.Leading Research, University Department and Clinical Pathology Department

The applicant has gained widespread experience as an administrator at various positions within University and in several national and international organizations and professional societies. Having headed two major national research projects in Finland (Papillomavirus Project and Breast Cancer Project, the applicant has shown his capability as a leader of large research groups. This experience has subsequently been extended to cover also the leadership of major multi-national prospective research projects funded by EC and comprising independent research groups in several countries. Indeed, coordinating these major projects is the main daily activity of the applicant at present (see 4.2.2.; 4.2.3.; 4.2.4.). During 1990-1993, I was one of the key designers of a new independent research institute (AIV Institute) in Kuopio University, as one of six Members of the Board, making the strategy as well as constructing the new building for the AIV Institute.

The applicant also has 10 years of experience as Professor and Chairman of the Department of Pathology, University of Kuopio, as well as Head of the Department of Clinical Pathology, Kuopio University Hospital. These positions cover the full spectrum of administration both at the University and University Hospital site. Further experience in administration of a clinical pathology institute was provided by the applicant's 16-year mandate as Director of a private pathology laboratory (owned by Finnish Cancer Society) with a substantial (>65.000 specimens) annual turnover. The single most important

responsibility of this laboratory was running the organized cervical cancer screening program in the area, of which I was personally in charge. The total personnel at these three institutions exceeded 60 people.

6.2.Leading the Medical Faculty

The applicant has also gained profound experience at the highest level of University Administration, while acting as the Vice Dean of the Medical Faculty, University of Kuopio between 1991-1994, and as the Dean of the Medical Faculty during 1994-1995. The single most important achievement as Dean was the self-evaluation of the Medical Faculty, based on interviews and site visits of all departments in 1994-95, published as a 100-page document entitled: Self-Evaluation of Medical Faculty, University of Kuopio (Syrjänen K., Kuopio University Press, 1995). Start of a profound renewal of the entire medical curriculum was my personal initiative as well. Linked with these leading positions were two important leaderships within the Medical Faculty: 1) Director of Research-Oriented Medical Curriculum (Doctoral School) and 2) Director of the Board and Scientific Director, Kuopio Cancer Research Center. Being different from the duties of the Faculty leaderships, these two positions covered yet two other important functions of the Medical Faculty, i.e. design of new orientation for undergraduate studies (to educate researchers) and coordination of multi-institutional research of the entire Faculty.

6.3.Research Collaboration with International Industry

Since the late 1980.s, the applicant has gained experience in administering (on behalf of his unit) a number of international, multi-centre research projects run by some international pharmaceutical companies, developing new therapies and diagnostic tests for HPV infections. These include e.g. Hoffmann La Roche, Wellcome, Abbot, Labsystems and Biohit. Indeed, some of my highest ranking papers have been published as a result of this international collaboration with other leading centres (item #259, 333). In 1996, the author was invited as member of the Scientific Advisory Board of NeoPath (Seattle, WA), manufacturing automated technology for cytological diagnosis and screening. More recently, the author joined the ICS, Ltd (International Cytopathology Services) team as a scientific director (parttime), responsible for designing novel strategies to promote the maintenance of high quality of the PAP smear in cervical cancer screening. Links to commercial enterprises are valuable in keeping on the edge of the latest developments of modern technology and novel concepts in diagnosis and treatment.

6.4.Organising International Congresses

Since the mid 1980's, the applicant has gained substantial amount of experience (in leadership and organisation) as an organiser of a number (26 until now) of international scientific conferences, as listed in CV. In acquiring such an experience, the most important conferences are those, where the author has had the main responsibility, e.g., being a congress president, or chairman of the programme committee. In this respect, three congresses are more important than the others: Workshop on Papilloma Viruses. Molecular and Pathogenetic Mechanisms. Kuopio, 1985; 19th European Congress of Cytology, Turku, 1991; and 16th International Papillomavirus Conference, Siena, Italy, 1997.

6.5.Consultant in research

Recently, I decided to share my widespread research experience and established a consultation company; SMW Consultants Ltd, to give assistance to anybody, but

particularly to the authors coming outside the English-speaking scientific community. Anybody who wants to exploit these services, covering the full range of items from study design to final report, is warmly welcome to visit the company website at: http://www.smwconsultants.fi. Feedback from innumerable satisfied colleagues particularly from Latin American countries makes all this highly rewarding.

7.LANGUAGE SKILLS

Finnish as the native. **Swedish** (the second official language), **English** (1st foreign), **German** (2nd foreign), **French** (3rd foreign), **Italian** (working language while in Italy), **Spanish** (fair understanding in spoken and written), **Portuguese** (fair understanding in written).

PEDAGOGICAL CREDENTIALS

1.TEACHING EXPERIENCE

The applicant has been involved in teaching both anatomy (macro & micro) and pathology at University level since a medical student himself (1970-1972)(Department of Anatomy, University of Helsinki), and 1979-1999 (Department of Pathology, University of Kuopio), respectively. The teaching positions held during these years are listed in the CV, and cover all levels of university teacher from a junior assistant, to senior lecturer and ending up as the full professor. In the field of pathology, these teaching positions (in Kuopio University) include Instructor (junior lecturer or assistant)(1979-1983), Senior Lecturer (1983-1985), Docent (1979-1989), and Professor (1989-1999).

1.1.Extent

At the Department of Anatomy, University of Helsinki, where the applicant was a junior assistant between 1970-1972, 100 medical and 30 dental students entered Anatomy twice a year. The courses run by the applicant included primarily macroscopic anatomy dissections. The first experience as a lecturer was obtained during this period (1971-1972), while giving a 30-h course of lectures (twice) on normal histology and embryology of the mouth (for dental students). At that time, all anatomy courses continued the full year, while new students entered twice a year. At the Department of Pathology, University of Kuopio, 75 students enter the course once a year. The Department organizes two courses a year: 1) General Pathology, and 2) Systematic (Organ) Pathology. Each one is composed of a) lectures, b) microscopy course (histopathology), and 3) autopsy demonstrations. The basic structure and the volume of the teaching remained essentially similar (repeated every year) during the entire period of 1979-1999, when the applicant has been involved in teaching (at various positions) in Kuopio University.

1.2.Level

The majority of the teaching at the Department of Pathology is at the under-graduate level (medical, dental and some paramedical students), as a part of their normal curriculum. In addition, the applicant did coordinate a regular post-graduate seminar series (CME) for physicians specializing in for pathology. A variety of specialized in-house courses were run at regular intervals at the Department as well. In addition to the regular post-graduate training at the Department, applicant has been a frequently used speaker in different post-graduate courses (more recently known as Continuing Medical Education, CME) in pathology and cytology in Finland, mostly organized by the national Societies. However, at the level of CME, the major activity of the applicant has been devoted to lecturing in CME courses outside Finland.

1.3.Experience Acquired

During the University career spanning a 25-year period, the applicant has acquired teaching experience in all currently available modes of teaching pathology. This includes anatomic dissections (1970-1972; Helsinki), autopsy demonstrations (1979-1985; Kuopio), microscopy courses in histopathology (1979-1985; Kuopio), lectures (1979-1998), including General and Systematic (Organ) Pathology. In addition, running and participating in different types of seminars, workshops, demonstrations etc., is familiar for the applicant, on several national and international occasions since the early 1980's.

In the CV, the extent of this activity is listed in the item: Invited Speaker or Guest Lecturer in International Congresses, Courses and Meetings. Since 1982, the applicant has been invited as a speaker (i.e., faculty member) to a total of 167 international congresses, courses or seminars. In most of them, the author has given more than just a single (sometimes up to 5) separate lectures.

An essential part of the applicant's experience as an internationally recognized teacher in **CME courses**, derives from the activities in three international organizations, with CME as the main or major goal: EUROGIN, ECHPV and IPVS. The most important CME events of EUROGIN (European Research Organization on Gynecological Infections and Neoplasia) (www.eurogin.com) include the organization of four major Congresses in Paris (1990, 1994, 1997 and 2000), all having CME training and scientific component equally balanced. ECHPV (European Course on HPV-Associated Pathology)(www.echpv.org), founded in 1991, has organized an annual CME course, usually participated by 100-200 specialists in different fields of HPV-associated diseases (gynaecology, pathology, dermato-venereology). IPVS (International Papillomavirus Society)(www.ipvsoc.org), is the formal continuation of an informal group of researchers, who have organised International Papillomavirus Conferences since the early 1980.s. An essential part of these annual conferences has been the pre-congress clinical workshop, a CME course, given by the highest level of international faculty. This workshop was organised by the author in 1997.

1.4.Responsibility

Professor and Head of the Department was the person-in-charge for the entire pathology teaching at the University. This entails continuous planning and renewal of the courses (lectures, practical courses, demonstrations), according to the requirements of the rapidly changing demands of modern medical learning. Special attention was focused on creating modern facilities and new instruments for teaching and learning pathology for medical (and paramedical) students at our Department. Among these are various computer-assisted (CR-ROM) learning methods and video-microscopy based teaching devices. This responsibility covers both the under-graduate teaching, pathology curriculum (specialist training) and CME at the University.

2.EXPERIENCE IN TEACHING ADMINISTRATION

2.1.Administration of Medical Faculty

During the 1990.s, the applicant has gained considerable administrative experience at the highest University level, while acting as the Vice-Dean and Dean of the Medical Faculty, between 1991-1995. In the latter position, the applicant was also member of the University Council. The Dean is the officer-in-charge of the entire field of administration of the faculty, including teaching, research and training, as well as CME. This experience is valuable in the administration of the single Department, with all different activities (teaching, research, pathology practice, CME, etc). In addition, the applicant has been member of Committee for Continuous Education of Kuopio University (1992-1998)

2.2.Education Administration

Reference was made above (1.4.) to the responsibility of the applicant as the person-in-charge of the administration of both under-graduate teaching and CME at Kuopio University. This experience as education administrator dates back to the period 1983-85, while as the Senior Lecturer and being the administrator of the General Pathology course

(both lectures, microscopy courses and autopsy demonstrations) at our Department. During the applicant's term as Dean, a new orientation was established among the undergraduate medical curriculum, aiming to training medical researchers (Research-Oriented Curriculum or Doctoral School.). The applicant was appointed as the first Director of this new school, having the administrative responsibility of setting up this new activity.

2.3.Board Examinations

As one of five Medical Faculties in Finland, Kuopio University also has the full curriculum leading to board-certified specialists in pathology and sub-specialists in neuropathology. This training of specialists is another responsibility of the Chair. As one of the six full professors of pathology in Finland, the applicant had (in his turn) the responsibility of organizing the national board examination for the candidates on completion of their training in the five Medical Faculties.

Towards the end of his 10-year presidency of the Finnish Society of Clinical Cytology, the applicant also designed the content of training and guidelines for the national examination, to make clinical cytology recognized as a special competence among pathology discipline in Finland. This work was based on the previous efforts made as President of the Finnish Association of Pathologists (1984-1989), aiming to get clinical cytology recognized as sub-specialty of pathology.

2.4.International Examinations

In 1994, IAC (International Academy of Cytology, USA) assigned the applicant the exclusive rights to arrange their international examinations (CT-IAC, CT-IAC-GYN, and FIAC) for cytotechnologists and cytopathologists in our country in Finnish language. For a small language group like Finnish, this is a particular privilege, previously granted to Japanese, German and Spanish (the other three non-English IAC exams).

3.TEACHING MATERIALS

3.1.Teaching Materials

During these years, the applicant has been involved in producing various types of teaching material in pathology, including the booklets on histological specimens, printed lectures, etc, as a part of normal activities of University teaching. During this period, large collections of slides from different fields of pathology have been gathered up. More recently, extensive sets of slides in the field of gynecological pathology has been produced by the applicant himself, utilizing sophisticated computer graphics, color scanners and high-resolution slide printer. This extensive set of slides is being used mostly for CME courses, and have been favorably evaluated by the audience and organizers in numerous international conferences.

The fast technological development is currently making regular slides soon obsolete as the tools of giving lectures and other demonstrations. Compared with conventional slides, presentations using video projectors connected to portable computers have definite advantages. The most obvious one is the possibility to create new (PowerPoint) presentations with very short notice, e.g., during the training event, if necessary. Another advantage is the possibility of including also videos within such presentations. The existing technology allows direct conversion of the graphic files of the previously printed slides into these PowerPoint slides, most comfortably stored on CD-ROM. Combined with color

scanners, this new technology offers powerful high-throughput tools in creating high-quality presentations at all levels of teaching pathology. The potentials of telepathology as a powerful new tool in teaching and quality control is fully recognized, while having had a change to closely follow the most recent developments during several visits in the institutes where this system is in regular use (e.g. RAMS, Moscow).

3.2.Textbooks

Despite the rapid development of different audio-visual techniques, conventional textbooks still are cornerstones in teaching and learning medicine. Producing these textbooks is one of the responsibilities of higher level teachers. During his University career, the author has produced two important textbooks for international publishers (1987 and 2000). The first one (item #338) is edited together with two internationally recognised authorities: Syrjänen, K.J., Gissmann, L. and Koss, L.G. (eds). **Papillomaviruses and Human Disease**. Springer Verlag, Berlin, Heidelberg, pp. 1-518, 1987.(ISBN 0-387-16341-7; 3-540-16341-7). On its publication, this book was the first systematic account for papillomaviruses and human disease, and as such received a favorable response among the discipline.

The second book was written together with a second author during 1996-1998, and published in 2000 (item #500): Syrjänen, K. and Syrjänen, S. **Papillomavirus Infections in Human Pathology.** J. Wiley & Sons, New York, pp. 1-615, 2000 (ISBN 0-471-97168-5). In the series of books published on papillomaviruses since the 1980.s, our new book is the first textbook-type authored (non-edited) volume, comprising 21 Chapters, covering the entire spectrum of HPV-associated diseases, and including over 4.300 literature references.

The third of the textbooks is entitled: **Gestione delle Pazienti con PAP Test Anormale. Athena Audiovisuals, Modena, Volume I: pp. 1-350, 2005** (ISBN 88-86980-52-3), edited together with S Costa. This volume comprises 12 Chapters covering the topics from oncogenesis to natural history, and finally to the strategies of cervical cancer control. This is the first comprehensive treatise on the subject published in Italian language and as such received a favorable feedback among the scientists in all Italian-speaking countries. The second Volume is currently under preparation.

3.3.Articles in CME Journals

During the past few years, a series of special journals have been founded, with the sole focus on publishing educational texts for CME purposes. The applicant has become a regular contributor in one of these new journals, **CME Journal in Gynecological Oncology**. The author has been repeatedly invited to contribute reviews on different subjects to this journal, which has received exceptionally favorable feedback among the specialists in gynecological oncology. Published as separate thematic issues, this CME Journal has become a new important tool in CME, reaching a wide readership among the professionals. This Journal recently invited me as an Associate Editor (2004), and more recently, **Associate Editor-in-Chief** (2006).

3.4.Video Recordings

Video recordings for educational purposes have become a regular part of the major international conferences, run by various film-video companies. Apart from these numerous direct recordings from the author's lectures, a series of separate recording sessions based on personal interviews have been arranged during these many conferences.

The first one was made by a recognized English recording company (Gardiner & Caldwell), during an HPV congress the 1985, and the latest one in Porto Alegre, Brazil, during the VI Brazilian Congress on STD/AIDS, 1996, where three separate recordings were produced.

3.5.Research Information in Popular Form

To promote the diffusion of the concepts of HPV infections as a STD as well as the importance of cervical cancer screening, among the general public, the Kuopio Project was active in disseminating the most recent research results through various media. Thus, in numerous occasions, such information in a popular form (usually based on interviews) was published in various media, including newspapers, weekly magazines, radio and TV. During these years, a huge number of material including clips from newspapers, weekly magazines as well as video-recordings from TV news and other programmes have been gathered up. During the many congress trips abroad, a number of similar opportunities to distribute this type of information via TV channels, radio and newspapers have been offered, most recently in Brazil, 2000.

3.6.Research Information and Teaching Material to Professionals

Within this category are included the numerous occasions to distribute the information of the ongoing research projects and its results in the form of more specialised (health) programmes in radio and TV channels. This category also includes short articles written in professional journals of different national societies and organizations, including the Finnish Cancer Society, distributed among their members. A sizable number of articles on different aspects of HPV infections have also been written by the author for the professional journals of the national societies (Finnish Medical Association and Medical Society DUODECIM), in Finnish language and included among the category Other Communications in the List of Papers. In this category is included a 40-page booklet: The **PAP Test Procedure**, produced with the Support of Leonardo da Vinci **Project of EC**, which I recently translated in Finnish (2000). The book was printed as 2.000 copies and distributed to all health centres in Finland. This book is intended for general practitioners and nurses, to describe the basic principles on the proper use of PAP test as a diagnostic and screening tool, and emphasizing the important quality control issues of the test. The impact of the booklet was tested by a mailed interview to the receivers, and the feedback was predominantly rewarding.

3.7.Web-sites (health pages)

The role of internet as a powerful tool in disseminating the information has also been realized by innumerable new internet companies focused on different issues of human health. Such .health. pages are particularly popular in the US, where people are traditionally very health-conscious. The applicant has made two contributions in producing substantial amount of material for the web-sites of two different companies: yourdoctor.com and International Cytopathology Services (ICS, Ltd). The former is available at web-site (www.yourdoctor.com), being targeted to both health professionals and non-professionals, and contain specialized information in all field of human health. The author's contribution, contains a detailed account (30-40 text pages) of different techniques used in diagnosis of HPV infections, the associations of the virus to cervical cancer, as well as use of optional screening tools, including HPV typing. The second one, completed during the year 2000 is even more extensive contribution, comprising the entire substance (>100 text pages) of the web sites of ICS, Ltd (www.icsglobal.co.uk), with

the main focus on emphasizing the role of high-quality PAP test as the only diagnostic tool with proven efficacy in cervical cancer screening. More recently, the websites of the applicant's personal company (SMW Consultants Ltd) were designed exclusively by the applicant, and these contain a useful piece of information related to different areas of biomedical research. These can be viewed at the address: www.smwconsultants.fi

4.PEDAGOGICAL EDUCATION

4.1.University Studies in Pedagogy

At the time of one's medical education, practically no pedagogical education was included in the medical curriculum, but the pedagogical skills had to be learned by practice. Indeed, the applicant realized this necessity of getting such a practice while being the 3rd-year medical student, and seeking into the position of junior assistant at the Department of Anatomy, University of Helsinki in 1970. This period of three years (1970-1972) as an instructor of anatomic dissections gave an excellent background and experience that was subsequently deepened while working as Senior Lecturer of Pathology in the 1980.s. Also the first experience as a lecturer (not the normal duties of assistants) is derived from that period, while giving a 30-h course of lectures for dental students in embryology and histology, repeated two times (1971 and 1972). Giving lectures at different levels (graduate, specialist training, CME) has subsequently continued almost uninterruptedly until present, for 30 years.

4.2.Other Pedagogical Training

While lacking a formal training in pedagogic, the applicant has gained his experience as a university teacher mainly by acting in different teacher positions for over 20 years (CV), most recently as Full Professor for 10 years (1989-1999). By far, the best training for the applicant to reach the current position as an internationally recognized lecturer in CME courses, is derived from the international forum. Since 1982, the applicant has been invited to give lectures in **215 international conferences** and/or CME training courses worldwide, and according to a conservative estimate, has given 2.5 to 3 times that number of individual presentations to audiences varying from <100 to over 2.000 people. This type of teaching experience cannot be replaced by any other type of pedagogical training or formal education. Something about the international recognition of my pedagogical skills can be determined from the growing number of invitations to these events, currently exceeding the total of 210.

5.DEMONSTRATED SKILLS OF TEACHING

The skills of teaching have been publicly documented by **demonstration lectures** given to Medical Faculties of Universities on the occasion of professorships and docent positions applied. There are several of these occasions since the late 1970's. In chronological sequence, these accepted demonstrations of teaching capabilities include the following:

- 1979 Kuopio University Docent in Experimental Pathology
- 1980 Kuopio University Docent in Pathology
- 1986 Oulu University Professorship in Pathology
- 1987 Helsinki University Associate Professorship in Oral Pathology
- 1988 Helsinki University Professorship in Cancer Biology