Editorial

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Research on papillomaviruses has travelled a long and winding road. To date, our growing awareness of the biology of these viruses has so far culminated in the definition of their critical role in the evolution of anogenital cancer in humans. Investigators are now considering the development of antiviral vaccines or other virus-specific strategies in order to interfere with this type of malignancy [for a review see ref. 1; Cowsert, this volume].

Several discoveries during the past 90 years form the basis of our current knowledge of papillomaviruses. The infectious nature of warts was established at the turn of this century and important observations such as the host specificity of human and animal papillomaviruses was discovered in the early days [for a review see ref. 2]. In the twenties, the principles of progression of benign papillomas into malignant cancer expedited by the synergism of chemical carcinogens were first described in the cottontail rabbit papillomavirus system. With the advent of modern technologies this and other animal models are still of great value for the study of virus-host interactions [see Brandsma, this volume]. The physicochemical characterization of virus particles and their DNA was initiated in the 1960s when virions were purified from skin warts in which efficient replication takes place [see Pfister and Fuchs, this volume]. It became apparent during this period that papillomaviruses stubbornly evade the investigators' curiosity by not replicating in cell culture. Since negative results often remain unpublished, it is unclear how many years of frustrating work have actually been spent at laminar flow benches before researchers reached the disappointing conclusion that the differentiation of epithelium, apparently critical for papillomavirus replication, cannot be fully imitated in culture. It was a milestone in

papillomavirus research when Kreider and colleagues succeeded in propagating HPV type 11 particles after grafting infected human tissue into nude mice [review by Brandsma, this volume]. As elegant and informative as this system clearly is, it comprises labor-intensive and sophisticated experiments and obviously does not permit the production of infectious particles at a preparative scale. The more recently introduced epithelial raft system may finally help to overcome what is still a major deficit in papillomavirus research [for a review see ref. 3; Chow and Broker, this volume]. Another promising avenue has been opened by the production of papillomavirus-like particles after expression of the structural proteins in recombinant vectors such as vaccinia [for a review see ref. 4; Pfister and Fuchs, this volume]. It can be expected that complete (i.e. DNA-containing and hopefully infectious) virions will soon become available by the aid of such systems.

Probably more than with any other virus systems, the advance of recombinant DNA technology in the 1970s boosted papillomavirus research. Investigation of the genome organization, the regulation of gene expression and the characterization of their products has resulted in the accumulation of a bulk of interesting information fostering our understanding of mechanisms of HPV-related car-cinogenesis [see Fuchs and Pfister; Stöppler et al, this volume]. It turned out that the genomes of different papillomaviruses are similar in their organization, thus permitting cross-hybridization at nonstringent conditions [5; Pfister and Fuchs, this volume]. In fact, many of the more than 70 HPV types have been identified after direct cloning of the DNA from infected tissues by using well-defined genomes or, more recently, general PCR primers

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as probes for nonstringent hybridization. This strategy permitted the detection of new viruses without prior purification of virus particles, which in most cases replicate at an extremely low level in vivo.

What have we learned by identifying so many HPV types? I remember that some time ago it was suggested that we should restrict ourselves to the characterization of one or a few papillomaviruses as was previously done when investigating the genetics of *Escherichia coli* bacteriophages. The argument raised against this position was that papillomaviruses are human pathogens and that we must first identify the most relevant agents before deciding which one(s) need(s) to be studied in detail. Following this advice led to the discovery of HPV 16 and other viruses related to the development of cancer of the anogenital and (as more recently found) respiratory tract. In fact, these viruses are now being studied by many laboratories [for reviews see ref. 6, 7]. In addition, DNA sequence analysis of a number of individual human and animal papillomaviruses and of intratype HPV variants isolated from different geographic regions is a powerful tool for studying the evolution of these viruses and their hosts [see Pfister and Fuchs, this volume].

Despite the firmly established role of HPV in human cancer and the growing understanding of mechanisms of cell transformation, many aspects of the biology of papillomaviruses remain enigmatic. Some of these aspects have been addressed in this volume: what is the natural history of papillomavirus infections; what can we expect from future epidemiologic studies; how do papillomaviruses manage to replicate in terminally differentiated cells; what are the prospects for anti-viral therapies [see contributions by Schneider, Cowser, Fisher, Chow and Broker]? The growing area of research on the immune biology of HPV infections as well as the anticipation of vaccine developments have recently been reviewed [1,8-10]. The article by Altmann et al. discusses immunological aspects specific to the control of HPV gene expression via cell-cell interactions.

I am grateful to my colleagues who contributed to this volume, which is intended to provide a snapshot of a rapidly moving field.

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