Looking Back on 45 Years of Research Activity

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It all started in 1969, when I interrupted medical school at Uppsala University for 3 years, starting as a PhD student at the Department of Medical and Physiological Chemistry (Fig. 1). My tutor had recently purified a vitamin A transporting low-molecular weight protein from human urine that turned out to be identical to the retinol-binding protein (RBP) concurrently discovered at Columbia University. My task was to find a more efficient way to purify RBP and to characterise its turnover in humans by injecting small amounts of radiolabelled protein into the blood stream. Turnover studies in healthy volunteers (including myself) showed a very short half-life of RBP, whereas in haemodialysis patients the half-life was markedly prolonged. This is consistent with a physiological model whereby the free fraction of plasma RBP – unbound to its complex partner thyroxine-binding prealbumin – is easily filtrated through the glomeruli and subsequently reabsorbed in the tubuli. This model explains why chronic renal failure leads to an accumulation of RBP (and vitamin A) in blood, whereas tubular necrosis yields proteinuria containing high amounts of RBP.

My thesis in 1972 encouraged future studies on the transport and function of vitamin A, an exciting research field not least in the mid 70s when cellular binding proteins for both retinol and retinoic acid were discovered and new retinoid analogues were being synthesised as promising remedies for both cancer, acne and certain disorders of keratinisation. No wonder I got interested in dermatology when choosing specialist training in 1976, especially as Professors Lennart Juhlin and Gerd Michaëlsson at the skin clinic in Uppsala were already pursuing research on vitamin A and zinc, and previous Swedish researchers had shown spectacular results of high-dose vitamin A therapy in a rare genodermatosis (Fig. 2). My aim was to establish a technique for measuring vitamin A levels in the skin and to screen patients with keratinising disorders, looking for abnormalities in the cutaneous vitamin A composition that might be related to the pathogenesis of the diseases and explain the frequent therapeutic success with high-doses of vitamin A or synthetic retinoids.

A new method called high-pressure liquid chromatography (HPLC) turned out to be a breakthrough in analysing minute amounts of retinoids in tissue extracts. Thus, in a superficial shave biopsy it became possible to detect as little as 1 ng of retinol in epidermis. Other retinoids were also separated on the HPLC column and could subsequently be collected from the outflow. This approach enabled me to identify a totally unanticipated form of vitamin A in human skin, viz. 3,4-didehydroretinol or vitamin A2. High amounts of this compound, previously known to occur in certain amphibians, were found in biopsies from psoriatic and Darier disease skin, possibly indicating abnormal vitamin A signalling in diseased keratinocytes.

In the beginning of the 1980s, together with 3 PhD students, Ola Rollman, Berit Berne and Hans Törmä, our studies were focused on the tissue distribution of both natural and synthetic retinoids in normal and diseased skin, on the interaction between UV irradiation and retinoids, and on the metabolism of retinol in cultured cells involving its delivery via RBP receptors to keratinocytes and subsequent transformation into 3,4-didehydroretinol, retinyl esters and retinoic acid. Although much was learnt from these studies, and our achievements were gratified with several reseach awards (Fig. 3), our main hypothesis that inborn errors of vitamin A metabolism might explain certain disorders of keratinisation was never verified.

Fig. 1. Experimenting as PhD-student in 1969 at the Department of Medical and Physiological Chemistry, Uppsala University.

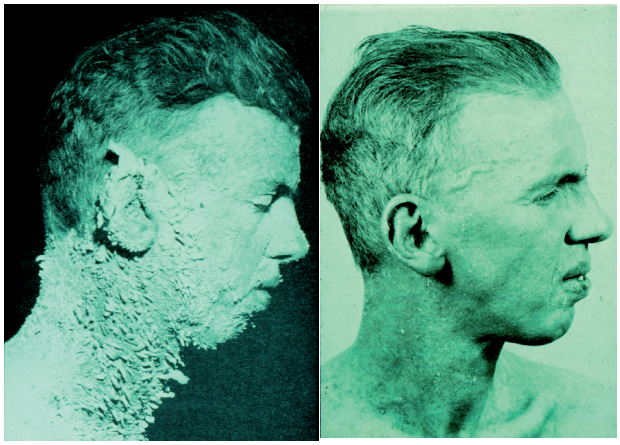

Fig. 2. Porcupine man syndrome: Before and after 3 monhts of high-dose oral vitamin A. From Lodin A, et al., Acta Derm Venereol 1966;46:412-422. This patient was still treated with retinoids when seen in Linköping. in 1988.

While surfing on a worldwide interest in retinoids both as dermatotherapies and as hormone-like factors controlling some aspects of epithelia differentiation via binding to the nuclear receptors RAR/RXR, we naturally became experts in using retinoids to treat especially severe monogenetic disorders of keratinisation, such as congenital ichthyosis. Hence patients with these rare diseases were increasingly referred to us for diagnostic and therapeutic purposes.

This interest continued when I was appointed Professor of Dermatology and Venereology at Linköping University in 1987. However, because of the emerging chlamydia and HIV/AIDS epidemics, my first task as Head of the department was to successfully fight for an increased budget for venereology. Teaching was another imminent task; Dr Chris Anderson had already prepared for a new problem-based curriculum in dermatology and working side-by-side with all colleagues at the department we enthusiastically launched these new ideas to the benefit of students. These and many other administrative tasks inevitably took time from my research. Luckily Hans Törmä also moved to Linköping for a couple of years and was instrumental in starting a new research laboratory, with Eva Andersson as technician. Later, Dr Inger Rosdahl, a melanoma specialist from Gothenburg, also joined our research group and eventually became my successor in Linköping.

Back in Uppsala in 1997, after my interest in molecular genetics had been spurred by a sabbatical year in Newcastle-on-Tyne learning new techniques in Professor Jonathan Rees's lab, a national referral Centre for Genodermatoses was started, involving the PhD students Marie Virtanen, Maritta Pigg and Agneta Gånemo, which is still in operation. Meanwhile, the aetiologies of a large number of monogenetic disorders of keratinisation and mechano-bullous diseases were unravelled, making it increasingly possible – via national and international collaborations (e.g. the GeneSkin EU project) – to correctly diagnose a whole range of skin disorders and to start looking for new, improved therapies. This research, facilitated by our increased understanding of the pathophysiology of skin barrier repair, has involved many more PhD students and is now lead by Hans Törmä as principal investigator.

In summary, over the years research activities have given me the advantage to go back and forth between patients and the lab bench, to work with colleagues in virtually all disciplines, and to follow PhD students from start to dissertation and beyond. I have also made many good friends at home and abroad, all devoted to the progress of our speciality and usually being members of societies such as ESDR, SID, EADV, AAD, EDF, and the Editorial Board of Acta Dermato-Venereologica!

Finally, I've had the great privilige of always working together with my wife (Fig. 4).

Fig. 3. Wearing wrong type of clothing when awarded the Marchionini Price at the opening of the WCD in Tokyo 1982 in front of old professors and members of the imperial family (black suit is compulsary!)

Fig. 4. No more working together in the clinic! Ever since 1976, Drs Carin and Anders Vahlquist have been working in the same departments. Now both are retired.