International Meeting on Classification of the Ectodermal Dysplasias
Charleston, South Carolina, USA – March 2008
Meeting Report by Angus Clarke (Department of Medical Genetics, Cardiff University)

I greatly enjoyed this meeting, held just 6 weeks ago in the elegant old Confederate capital. Thank you to the NFED for holding it and to YOU (the ED Society) for covering my travel costs!

The idea behind this event was that the advances in molecular genetics from the past two decades have given us the opportunity to rethink the whole idea as to what is an Ectodermal dysplasia (ED).

One example to help explain this is given by the EEC, Hay-Wells and Rapp-Hodgkin syndromes. These have been understood as distinct types of ED; do we think about this differently because of the finding that the three ‘syndromes’ – the phenotypes – can all be caused by mutations in the same gene (the \textit{p63} gene)? Does this make them the \textit{same} condition? Or is it still important that the details of the phenotypes associated with mutations in the \textit{p63} gene are still different?

Another example concerns the \textit{NEMO} gene, found on the X chromosome. Some mutations in this gene are lethal to the affected male embryo early in development and are associated in the surviving female with the X-linked dominant condition, 'Incontinentia Pigmenti'. Other ‘milder’ mutations in the same gene can be found in male infants who have ‘X-linked Hypohidrotic Ectodermal Dysplasia with Immunodeficiency’ and in their (usually unaffected) healthy female relatives who carry the condition. Are these two distinct conditions or one?

Each example – and there are many more – can be discussed and debated. But is there a helpful framework for approaching these questions? If we get it right, will that make research more effective at understanding how the genes interact to develop the normal ectoderm – and how to help this process when it does not work so well, by finding useful treatments for ED?

The meeting consisted of a series of talks by the most eminent clinicians and scientists investigating the EDs, with each talk followed by a period for discussion. There was a definite sense of progression over the three days of the meeting, as our initial ideas were aired, debated and improved, although we did not arrive at a single position of consensus. We reviewed the types of ED for which the relevant genes are known and discussed how we could best group the EDs into different categories. Some of those debating the issue were clear that our classification of the EDs should be as rational as possible and determined by the molecular nature of the ED involved. Others insisted that any revised scheme of classification must work well for everyday medical practice in the clinic.
We heard about the new World Health Organisation scheme for assessing and recording specific functional impairments. There was not enough understanding of the purpose of this classification for us to make real progress with the multidimensional approach to categorising impairments. Other topics covered included the molecular genetic basis of tooth number (and missing teeth, i.e. hypodontia).

We heard an update on the project of Olivier Gaide, who developed a system using the EDA1 gene product to correct the X-linked HED in mice (Tabby) if the treatment is started at a young enough age. There are a number of issues still to resolve, however, including the potential hazards of using powerful molecules on humans during fetal life in utero (in humans, the treatment would probably have to be used before birth to be effective in stimulating the development of sweat glands) and how to decide what other animal models to test this on before attempting it in humans. Despite these issues, it may well be possible to find a route through the regulations on drug development because a special case may be permitted on account of the rarity of the XHED.

In the case of other EDs, the difficulties in devising a safe but effective treatment seem more difficult, as it might require the therapy to introduce the correct copy of the gene to where it would be needed. This will be much more difficult than giving a few doses of the gene product.

At the end of the meeting, we first attempted to draw up a helpful definition of ‘ectodermal dysplasia’ but did not manage, although the practical value of a definition would be great. We discussed various proposed definitions with vigour but did not reach a consensus - perhaps some fresh opinions might succeed later. For example, how many non-ectodermal dysplasia signs can there be before one concludes that the affected person has a distinct and different type of disorder, not an ED? We decided to leave this and related tasks to a small committee .... Let us hope that they are successful.