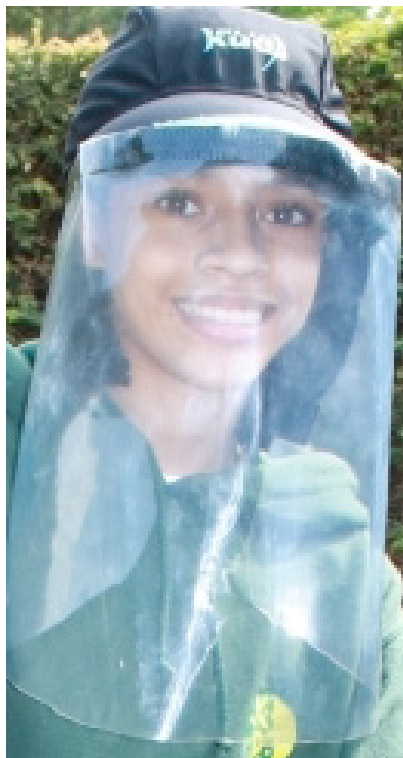


# Transforming the diagnosis and clinical management of xeroderma pigmentosum



‘[Professor Lehmann] brought science to our families and made us more connected with what is going on with our children.’

Founder of the UK XP support group



Research at Sussex has revolutionised the clinical diagnosis and management of xeroderma pigmentosum (XP). Sufferers of XP are extremely susceptible to sunlight-induced skin cancers and in some instances neurological problems. The development of a cellular diagnostic test, which is now an integral part of patient management at a multidisciplinary clinic in London specialising in the treatment of this condition, has improved diagnosis and patient management and quality of life for this rare but debilitating and dangerous disorder. The impact of this work in the UK has been particularly significant, with approximately 90 per cent of the country's XP patients now being seen at the London clinic.

## Overview

Xeroderma pigmentosum, Cockayne Syndrome (CS) and trichothiodystrophy (TTD) are genetic disorders characterised by a deficiency in the ability to repair damage to the DNA following exposure to ultraviolet (UV) light. In XP, all direct exposure to sunlight, even small amounts, should be avoided. Sufferers of XP are highly susceptible to the development of skin cancers – metastatic malignant melanoma and squamous cell carcinoma are two of the most common causes of death among XP patients.

Despite the devastating effects of XP on affected individuals (primarily children) and their families, access

**Professor Lehmann has played a pivotal role in establishing a multidisciplinary xeroderma pigmentosum clinic at St Thomas' Hospital, London. The attendance of patients at the clinic has resulted in improved UV photoprotection, especially for children: in 60-75 per cent of UK families with XP children, patients wear a UV visor. Lower image reproduced by kind permission of Alex and Sandra Webb.**

to adequate clinical care has been unsatisfactory due, in large part, to a lack of clinical expertise. Since 1975, the work of Professor Alan Lehmann (Research Professor in Molecular Genetics at the Genome Damage and Stability Centre, University of Sussex) has focused on the study of the cellular and molecular basis of XP and related disorders. His group was the first to show that a variant form of XP was deficient in the ability of cells to replicate DNA that has been damaged by UV light and that CS cells failed to restore RNA synthesis (critical for the production of new proteins) after UV irradiation. In addition, TTD cells, like XP cells, were shown to be defective in the ability to remove UV damage from cellular DNA.

This work, by Professor Lehmann and others, uncovering the cellular deficiencies in DNA repair as the basis for these disorders, led to the development of specific cellular diagnostic tests. More recently, genetic research in Professor Lehmann's laboratory has identified causal mutations that occur in many patients – defects in any of eight genes can result in XP. With one of these genes (XPA), they found that genetic defects can result in a variety of clinical outcomes and that the exact site of the mutation in the XPA gene determines the clinical features. In addition, patients defective in the XPD gene are generally severely affected with both skin and neurological abnormalities. However, a particular XPD gene mutation found in patients with mild symptoms and no neurological problems has allowed for a more accurate and optimistic prognosis. Such detailed genetic studies allow for more exact prognoses in some patients and improved postnatal and prenatal diagnosis.

## Achieving impact

Lack of clinical expertise and poor access to appropriate clinical care were major issues for sufferers of XP, both in the UK and globally. The impact of Professor Lehmann's work in improving the management of XP has been significant and has involved two major breakthrough areas.

The development of an accurate diagnostic test allows unambiguous confirmation or exclusion of a clinical diagnosis, and accurate diagnosis

has proved critical for optimal patient management, both in the UK and internationally. Between 2008 and 2013 the test was used to diagnose about 60 cases of XP, CS and TTD from 300 samples that were referred. In the other cases the diagnosis was excluded. In addition, over 70 prenatal diagnoses have been made in CS families.

Professor Lehmann also played a pivotal role in establishing a multidisciplinary clinic, initially at Southlands Hospital in Worthing with Dr Arjida Woollons and subsequently, since 2008, at St Thomas' Hospital, London, under the clinical leadership of Dr Robert Sarkany. With the support of funding from the NHS National Commissioning Group (NCG), the clinic is held every two weeks, allowing three to four patients to spend an entire day at the clinic to receive detailed examination and advice from different clinical specialists, including genetic expertise and guidance from Professor Lehmann as Consultant Scientist. The attendance of patients at the clinic has resulted in improved UV photoprotection, especially for children: in 60-75 per cent of UK families with XP children, patients wear a UV visor and UV protective film has been installed in both their homes and schools. Skin cancers are identified and excised at a very early stage and there has been increased awareness of the importance of eye protection.

Professor Lehmann's work shows the potential for a body of research to penetrate deeply into a specific disease area. Although a relatively rare condition, almost all of the UK's XP patients (approximately 90 per cent; currently 78 patients) are now seen regularly at the clinic. The impact of the clinic on patients, their families and on clinicians who manage these disorders has been profound. The founder of the UK XP support group described how the multidisciplinary team provided an 'excellent' patient experience and how '[Professor Lehmann] brought science to our families and made us more connected with what is going on with our children'.

Dr Sarkany who heads the clinic at St Thomas' Hospital has reported that the NHS NCG, which annually audits the service, has: 'commented in each audit on the excellent and symbiotic

relationship between Professor Lehmann's team of research scientists and our multidisciplinary clinical team, which contributes to the standard of patient care in this clinical service'.

## Future impact

Following on from the success of the XP multidisciplinary clinic, a similar clinic will be established, hopefully in 2015, for Cockayne Syndrome. Although the molecular basis for the disorder is quite similar to that of XP, the clinical features and clinical needs are quite different. Again, Professor Lehmann and his diagnostic work will be an integral part of the clinic.

## Funding and partnership

Professor Lehmann's work has been funded by the Medical Research Council and the European Union, and his diagnostic laboratory is currently funded by the National Commissioning Group of the NHS, as part of the XP clinic.

## Working with us

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