Ehlers-Danlos syndrome

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The Ehlers-Danlos syndromes (EDSs) were originally described by Ehlers in Denmark and Danlos in Paris in 1898 and 1908, respectively. They had both published individual case studies in which the common factor was laxity of ligaments leading to joint hypermobility and hyperextensibility of the skin. The choice of the name of this eponymous disease had been made by Dr Parkes Weber, an eminent London physician in the 1930s, who had a penchant for eponymous diseases, having had no less than seven attributed to himself, at least in part. Unfortunately, this was before the age of a computerised literature search, and Parkes Weber had inadvertently overlooked the very first description of EDS which had been made by Tchernabogov, a Russian dermatologist, whose description was published in 1891 and remains one of the best descriptions of EDS in the literature.

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How a little-known study of Peter's and mine from the 1960s transformed the process of recognition of stretchy skin in the Heritable Disorders of Connective Tissue …

It is an enormous pleasure and honour to be invited to contribute to Peter Beighton's Festschrift. *Peter and I go back almost half a century. We met in 1968. He was then working as a registrar in medicine at St Thomas' Hospital in London, and I was in training in rheumatology with the late Prof. Eric Bywaters, Professor of Rheumatology at the Royal Postgraduate Medical School, Hammersmith, UK. Peter subsequently held a fellowship with the late Victor McKusick, the father of modern medical genetics, at the Johns Hopkins Hospital, Baltimore, USA. Victor was the author of the classic monograph* Heritable Disorders of Connective Tissue.

While at St Thomas's, Peter decided to investigate the Ehlers-Danlos syndrome (EDS) as a doctoral project. He set about this task with characteristic fervour, and collected and painstakingly described a series of EDS patients by single-handedly combing the country. In an impressive feat, he rapidly identified 100 cases, whom he described in a series of 13 seminal studies, all of which (with one exception) were published between 1968 and 1970. EDS patients were looked at in depth from every angle. The outcome was truly impressive. His amazing productivity was summarised in a monograph published in 1970, which reflected his prolific writing of that period.

Background

My meeting Peter was not in any way a chance happening. Not long after I had commenced my post as registrar in rheumatology, it was suggested to me by my professor that I try to develop a method for measuring skin change using a suction cup in scleroderma, which

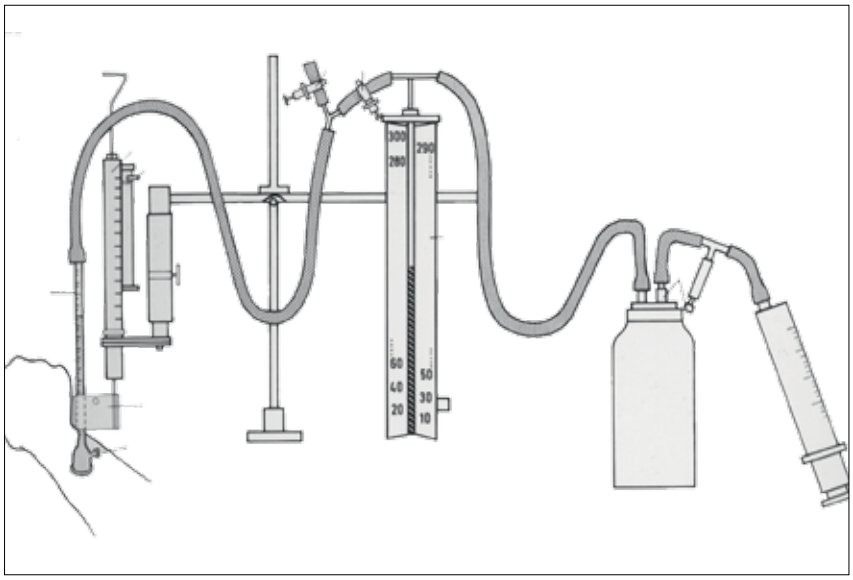

Fig. 1. Apparatus for measuring skin elasticity in vivo, circa 1968.

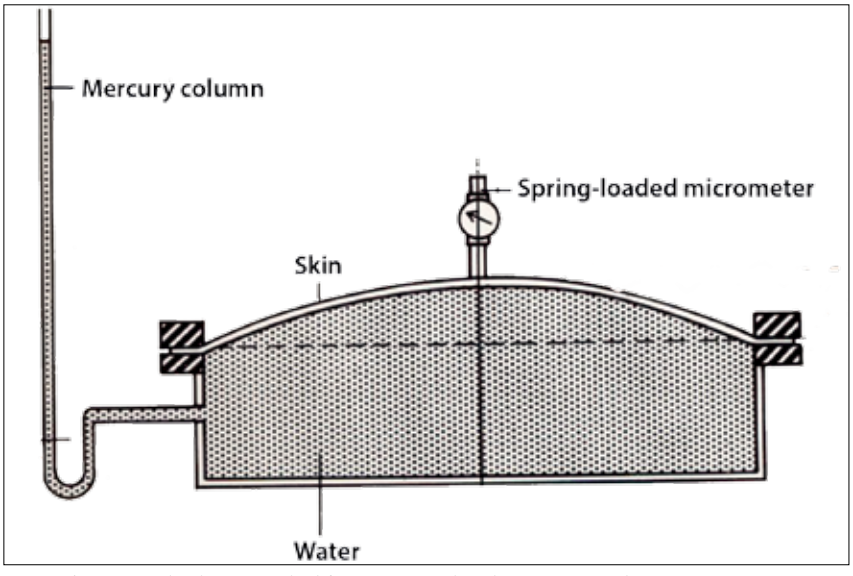

Fig. 2. The in vitro diaphragm method for measuring skin elasticity, J C Dick, circa 1951.

is characterised by a leathery appearance and texture of the skin due to a systemic inflammatory disorder of unknown aetiology. The idea was to construct a glass cup 2 cm in diameter that could be applied directly to the skin. A water displacement method was used to measure the resultant deformation of skin as it was sucked into the cup by observing the rise in the column of water in a tube (attached to the dome of the cup) in response to a series of negative pressures delivered to the top of the tube, using a sphygmomanometer in reverse (Fig. 1).

In effect, this was an application (in reverse) of the diaphragm method of measuring skin elasticity in vitro, which had been earlier developed by Prof. J C Dick, a physiologist from Glasgow, Scotland (Fig. 2).

Because the skin in scleroderma is adherent to the underlying tissues, it was not possible to raise a dome into the cup on the application of negative pressure: therefore it was not possible to use this method for measuring skin elasticity in scleroderma. However, it did prove a satisfactory method for measuring skin elasticity in vivo in those conditions where the skin is not adherent to the deep tissues. Then a stress-strain curve could be drawn for human skin in vivo. The first task was to validate the system using artificial tissues, different types of rubber sheeting, and different sizes of cup. This proved successful. A series of studies on normal subjects of both genders and of different ages was conducted.[1] For the purpose of this article, it suffices to say that in the realm of the heritable disorders of connective tissue (HDCTs), the technique provided for the very first time a means of observing how skin stretches in patients in EDS and how the stretching process differs from that in normal subjects.[2] From the illustration in Fig. 3 it is clear that the difference lies in the first phase of the J-shaped stress-strain curve attributed to the taking up of slack rather than the linear second phase, the gradient of which by definition represents the elastic modulus of human skin in vivo.

It will not surprise this readership to learn that after its publication in 1969, the paper disappeared without trace and was entirely forgotten by the medical and scientific community. Years later, I learnt to my amusement that the cosmetics industry had used the method as the gold standard by which to compare the results of more modern methods of measuring skin elasticity for use of testing their products!

But for me the outcome was different. For the past 45 years I have routinely used the knowledge gained from this early study to develop a clinical test that has the capability of distinguishing between 'stretchy' and normal skin and I use it every day on every patient I see. I like to call it the 'rubber glove skin test' (Fig. 4). It is simple to perform. I raise a skin fold on the dorsum of the hand. In normal skin, the stretching process is limited to the area of the fold itself. In 'stretchy' skin the stretching process is seen to extend to the wrist or beyond in one direction and around the dorsum of the hand in the other. This effect is not limited to EDS. It is also seen in Marfan syndrome and other HDCTs. For me, the test indicates the presence or absence of an HDCT, but not necessarily revealing which one.

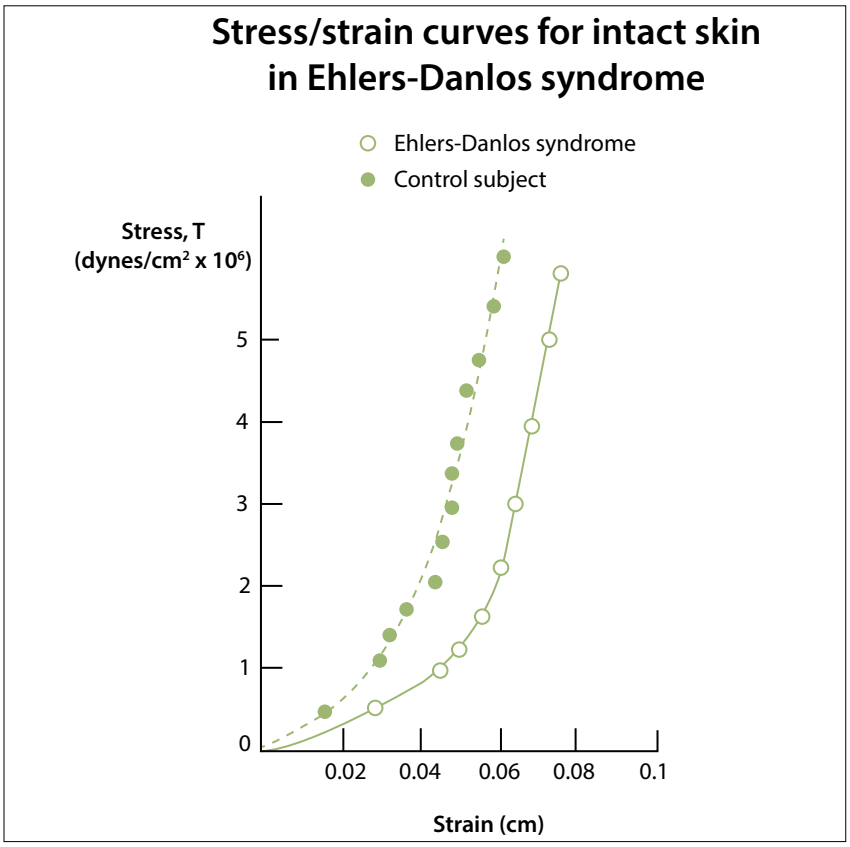

Fig. 3. Comparing the stress-strain curve of skin in vivo in a patient with EDS and in a control.[2] *(Reproduced with kind permission from the* Annals of the Rheumatic Diseases.*)*

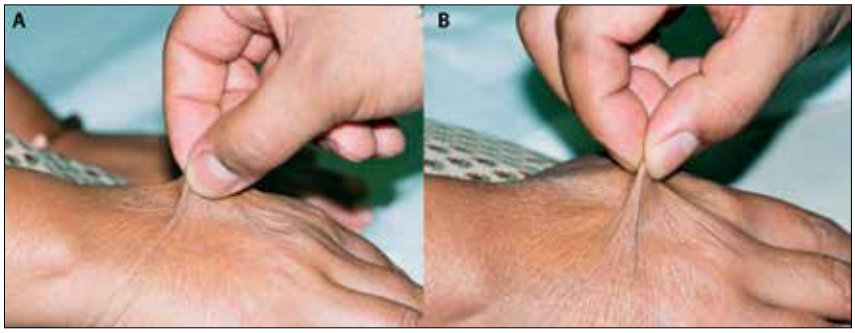

Fig. 4. The rubber glove skin test on normal skin (A and B).

Without Peter, this simply would not have been possible. It is worthwhile mentioning that all this work took place before Peter set sail for the southern hemisphere!

Peter, it was you who attracted me towards connective tissue disease research. You were a great influence on my career, and it has been a great pleasure and privilege to work with you for what amounts to just short of half a century. I thank you!

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2. Grahame R, Beighton P. Physical properties of the skin in the Ehlers-Danlos syndrome. Ann Rheum Dis 1969;28(8):246-251.