

Emery-Dreifuss Muscular Dystrophy (EDMD or EMD)

We are planning a new series of articles in which we ask famous neurologists to describe neurological disorders that they have either discovered or to which they have made a major contribution. In this, the first of the series, we invited Professor Alan Emery to describe the story leading to the first description of Emery-Dreifuss muscular dystrophy. His account combines the scientific and human side of neurological research and acts as an inspiration to all those embarking on or involved with such research. - Roger Barker

'As good luck would have it!'

Shakespeare. The Merry Wives of Windsor

I qualified in medicine rather late in life at the age of 32, having first served in the Army and then having taught for several years. Thus to me career opportunities in medicine at my age seemed a little restricted. I therefore seized an offer in 1961 of a travelling Fellowship to go to Johns Hopkins University to study the then burgeoning new specialty of Medical Genetics. I registered for a PhD degree with the aim of researching the clinical and biochemical aspects of muscular dystrophy.

This decision had been partly influenced by advice when I attended a demobilisation course just before leaving the army for civilian life. Most attending the course wanted help about possible future careers. The lecturer repeatedly emphasised, in a rather cynical way we thought at the time, that it would be best to choose an unpopular field because there would then be less competition! I'm not certain how true this is in general, but certainly in my case it proved good advice. I was attracted to muscle disease because there seemed very little interest in the subject among most clinicians at the time yet a lot of patients with these diseases were attending the neurology clinic where I worked. Furthermore muscle diseases were already recognised to be usually genetic but little else was known about them. It therefore seemed from all points of view to be attractive to someone who wanted a career in research and in medical genetics. It's also possible that I may have been somewhat influenced by having had osteomyelitis in my leg in early childhood, in the days before antibiotics, and spent more than two years wearing a calliper - or 'irons' as they were then called

I became particularly interested in Duchenne, the commonest form of muscular dystrophy. In order to identify genetic factors in the disease however it was necessary to study extensive families with several affected males. But such families are very rare because affected boys rarely survived beyond adolescence and therefore did not transmit the disease. I was therefore very excited when I read in a scientific paper published at the time of an extensive family in Virginia affected with what the authors considered to be merely a mild form of Duchenne muscular dystrophy.¹ Some of the affected males in the family had survived to middle age and had had children! I wrote to the senior author of the paper, Dr. Fritz Dreifuss in Virginia, and asked if he would have any objection to my driving down to see the family. He was delighted to find someone so interested in the disease. All the family members, except one, lived within easy driving distance of each other and Dr. Dreifuss said he would arrange for them all to meet me in the local school house where the senior affected member of the family was a teacher. I could see the various members of the family, examine them and as he said 'do whatever else you like!'

In those Elysian days it was still possible to carry out an entire research project on one's own. So I put together in my station-wagon all the equipment I would need. This included the usual instruments for doing a clinical exami-

nation such as a stethoscope, tendon hammer, and ophthalmoscope. I also took along my camera, books of colour plates used to assess colour blindness, equipment for blood sampling for the determination of blood groups back in the hospital, a centrifuge for spinning the blood samples, a small electrocardiogram (ECG) machine for monitoring cardiac activity and finally a rather old-fashioned spectrophotometer and the necessary chemicals in order to measure creatine kinase levels in blood. The latter had just been introduced by Japanese scientists as a valuable diagnostic test for muscular dystrophy and I was keen to use it on the various members of the family. The car was so full that there was hardly room for my personal belongings - and I spent some time carefully checking and re-checking the equipment. This was going to involve a round-trip of over a thousand miles and there might only be this one opportunity. I also needed good maps as the family lived in a remote area of the Appalachian Mountains close to the borders of Virginia, Kentucky and West Virginia, a part of America with which I was not at all familiar.

The small community in which the family lived turned out to be very remote indeed and it took me a day and a half to locate it. Fortunately I'd left plenty of time and arrived on the Friday afternoon, which I spent with the school teacher. What a very delightful man he was. He had obviously been on the lookout for my arrival and as I parked on the grass in front of the small schoolhouse he came out to shake hands. I shall always remember his greeting because as he walked toward me he exhibited a gait which is almost diagnostic of the disease. He was in his 50s and walked with a waddling gait. But apart from lordosis, he also walked with both elbows bent. He gave every appearance of a cowboy in a Western movie, who strolls out with both hands resting on his revolvers! I came to refer to this as the 'cowboy gait' and it seemed even with my limited experience, to be unique to this disease.

He invited me to his home for an evening meal and so we could get to know each other better. One of the great attractions of medical genetics was to visit families in their own homes. Unfortunately this is nowadays not done so much. As we sat and drank coffee, and later a glass of 'Wild Turkey', our talk turned to the family's origins. They were very proud of their ancestry having descended directly from early English and French settlers. At the time a hobby of mine was recording old folk songs and one of the family members obliged by singing an old song, passed down through the generations with a refrain about 'good Queen Bess'. They had no idea who this referred to, but from the lyrics it seemed to me to refer to Queen Elizabeth I of England. I still cherish these recordings but unfortunately the quality is poor. I'm sure this region of the US is a wonderful source of folk songs just waiting to be researched - or perhaps it has, and I've no doubt missed it....

I soon fell asleep that night, probably aided by the Wild Turkey, and the following morning turned up at the school house all ready to start. The entire family had already been marshalled there and in some ways the scene resembled a church fete run by the Women's Voluntary Service back home. Screens had been brought as well as a couch, a desk



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The late Dr. Fritz Dreifuss.



Emery Self Portrait

for me to write at and various tables for the equipment. I began by drawing up the family tree in chalk on the blackboard. We would use felt pens and a special laminated board nowadays. It was a great help to have everyone there so all the facts could be checked. A few details were added but it was essentially the same as the published pedigree. Then began the laborious job of meticulously examining everybody in the family including the unaffected females who, from the pedigree, clearly carried the abnormal gene. The blood samples were each placed on one side to be analysed later that night.

Eventually in the late afternoon I had finally made notes on everyone. This included information on eight affected males (one of whom had died some time previously) ranging in age from 11 to 55, and some eleven female carriers. The disorder was clearly inherited as an X-linked recessive trait. I had a hasty meal at one of the family member's homes and then returned to start analysing the blood samples for the enzyme creatine kinase.

These were good, kind and hospitable people and they wanted me to delay my return so they could show me something more of the countryside. However I was anxious to get home and study the results of my efforts but promised to return later. In fact a few months later I did return to fill in some gaps in the information I had gathered on my first visit. And returned again some 25 years later to a great family welcome, when they made me feel almost as if I had come home!

When I returned to the department I began to put together all the information I had collected and it slowly dawned on me that, for various reasons, this disease was perhaps a clinically distinct condition and may not have been described previously. It was clearly not Duchenne muscular dystrophy or for that matter any of the other forms of muscle disease I had seen or read about. I decided to present the results at one of our research seminars. I had expected, with the naiveté of youth and inexperience, that the findings would be greeted with great excitement. But I was disappointed. There was of course polite interest but that was all. In retrospect I think it was largely because perhaps I was the only one in the Department at all interested in muscle diseases! In fact it was several years later when I had returned to England that I had the courage to submit the details for publication in a journal specialising in neurological and neuromuscular disorders.² A little interest was shown and a few people wrote to me for reprints, but that was all. However in my medical work I kept a watchful eye open for other affected families and gradually my files on the disease increased. But it was not until 20 years after my first foray into the Appalachians that the reality of the disease as a distinct entity began to be accepted. This resulted from a scientific paper written by the eminent New York neurologist, Lewis Rowland, in 1979 in which he described a case and drew attention to our first description of the disease, and suggested the eponymous name Emery-Dreifuss muscular dystrophy.³ An autosomal dominant form is now also recognised⁴ and though some slight clinical differences have been suggested, both forms of the disease are characterised by:

1. *early* contractures, often *before* there is any significant weakness, of the elbows, Achilles tendons and postcervical muscles (with limitation of neck flexion but later forward flexion of the spine becomes limited);

2. slowly progressive relatively mild muscle wasting and weakness with a humeroperoneal distribution (i.e., proximal in the upper limbs and distal in the lower limbs) early in the course of the disease. Later weakness also affects the proximal limb girdle musculature;

3. most importantly a cardiomyopathy usually presenting as cardiac conduction defects ranging from sinus bradycardia, prolongation of the PR interval to complete heart block (Figure 1).

The genes and their products for both forms of EDMD have now been identified. The STA gene at Xq28 encodes for a nuclear membrane protein designated 'emerin',⁵ and the gene LMNA at 1q21 encodes other nuclear membrane proteins, lamins A/C.⁶ Mutations of the latter gene are now also associated with at least seven other disorders as well (Table 1).⁷ How the STA and LMNA genes regulate cardiac conduction, the most important aspect of the disease, is as yet completely unknown. Yet this could have far-ranging implications in cardiology in general.

Some time ago I began to search the old medical literature to see if this disease had ever been described previously. I had almost convinced myself that our description was unique when my attention was drawn to an obscure publication in French in 1902. In this report from the Salpêtrière Hospital in Paris, two brothers were described who, though there was no mention of muscle pathology or heart involvement, which is a very important manifestation of this form of muscular dystrophy, may have had the same disease we had described.⁸ Nevertheless as the French might say: Quoi de neuf? Rien de neuf!

Table 1: Clinical disorders resulting from different mutations of the LMNA gene

EMERY-DREIFUSS MD	(AD)
LIMB GIRDLE MD TYPE 1B	(AD)
DILATED CARDIOMYOPATHY & CONDUCTION DEFECTS	(AD)
ATRIAL FIBRILLATION ± DILATED CARDIOMYOPATHY	(AD)
PARTIAL LIPODYSTROPHY	(AD)
CHARCOT-MARIE-TOOTH TYPE 2	(AR)
MANDIBULOACRAL DYSPLASIA	(AR)
PROGERIA (?WERNER'S SYNDROME)	(AR)

(MD: MUSCULAR DYSTROPHY; AD: AUTOSOMAL DOMINANT; AR: AUTOSOMAL RECESSIVE)

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Figure 1: An original family member age 18 and again at 45. Note evidence of heart block at the later age.

