Editorial

Trisomy 21: Fifty Years of History

It is safe to say that in this day and age every reader of this journal and a significant portion of society recognize the name 'Down syndrome' and know that it is named after John Langdon Down. They are also aware that he was the first to describe this syndrome as a distinct medical entity, back in 1866, in Victorian England. Dr. John L Down, a highly respected physician of his era, simply listed a series of physical traits normally associated with this syndrome. He spoke of a 'weak pulse', of delayed physical and mental development, of characteristic Oriental-looking facial traits, and so forth. It was also he who coined the term 'Mongolism' for this disorder; children with this condition were occasionally called 'unfinished children', based on the belief that human races corresponded to different stages in the evolution of the human species and that they were throwbacks, as if there were something lacking in their normal development. This echoed the theories voiced at the time by Langdon's countryman and distant relative, Charles Darwin. The syndrome was subsequently ascribed to a number of causes, including infectious diseases, parental drinking, and other disorders of the times.

In the early twentieth century the relationship between Down syndrome and maternal age became established, as well as the fact that the children tended to be the youngest of usually large broods; these factors often converged. It was also in the twentieth century, specifically in the 1930s, that a possible link to some kind of defect in genetic information was first proposed. A gap or defect in genetic information was suspected, but laboratory techniques could not yet provide accurate chromosomal tests, and even after these became available they remained very crude, to the point that for several years humans were thought to have 48 chromosomes. Only in 1956, when it was established that there are 23 pairs, could it finally be known that the right number of chromosomes was 46.

Taking advantage of recent developments in human karyotyping, a French researcher, Jérôme Lejeune, working in Paris, and Patricia Ann Jacobs, a less-known English researcher working in Edinburgh, almost simultaneously described the chromosomal origin of this syndrome, namely, the presence of a third chromosome 21. That was when it was definitively classed as a genetic syndrome.

We celebrate the 50th anniversary of this important breakthrough this year, rather than last, because the discovery was published in 1959 (J. Lejeune, M. Gautier, R.A. Turpin: "Le mongolisme, maladie chromosomique (trisomie)". *Bulletin de l'Académie nationale de médecine*, Paris, 1959, 143, 256-265) (Jacobs P.A., Baikie A.G., Court Brown W.M., Strong J.A. "The Somatic Chromosomes in Mongolism". *Lancet*. 1959 Apr 4; 1(7075):710), so the scientific world first heard about it a year later.

Jérôme Lejeune was a participant at the International Conference held by the FCSD in 1989, and told us the story of his discovery. He said it happened during a trip to the United States. Shortly before his departure, one of his coworkers handed him several photographs of 'metaphases' (chromosomes) taken via microscope for a number of cases of Down syndrome. We should note at this point that until computers came to be used to obtain a karyotype (a set of chromosomes sorted by size), chromosomes were photographed directly from the microscope and the pictures cut out and pasted on cardboard; this is still done today in some laboratories with very limited resources.

Lejeune slipped the pictures into his briefcase and went over them during the flight; that was when he realized that every photograph, and hence every cell studied, had 47 chromosomes, with 5 chromosomes in group G if the individual was a girl, and 6 if it was a boy. Before the banding technique was developed in the early 1970s, chromosomes were grouped by size in groups from A, the largest size, to G, the smallest. Group G comprised chromosomes 21, 22 and Y, but they could not yet be told apart, so Down syndrome was described as a group G trisomy that might be attributed to the 21 pair or the 22 pair. Subsequently Down syndrome was arbitrarily assigned to chromosome 21, which turned out to be the smallest one so it ought to have been number 22.

When the scientific community drew up standards for karyotpying by chromosomal size, the link between Down syndrome and trisomy 21 was respected, and in fact the two terms were established as synonymous with each other. By way of anecdote, Jérôme Lejeune used to exact a symbolic fine of one franc from any coworker who referred to the syndrome as 'Mongolism' rather than 'trisomy 21'.

Other researchers would later describe less-frequent forms of DS, such as translocations and mosaicisms. The DNA and individual genes comprising chromosome 21 have also been studied in detail.

Down syndrome is well known as a clinical entity, but research on its origin and the effects of the triple dose of genes are far from close to yielding all they can deliver. After half a century of trisomy 21, beyond recognizing the role of those early pioneers in research, we would like to spur on new generations of researchers to work hard and uncover the hiddenmost aspects of this syndrome in order to avert it or palliate its adverse effects as far as possible.

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