Chapter 1. Historical context and original description

In the late 1950s, it became possible to examine the number of chromosomes using cultured bone marrow cells. By that time, it was also known that the normal human cell contained 22 pairs of autosomal chromosomes and two sex chromosomes. Based on chromosome size and the location of the centromere, chromosomes were assigned to general categories A through G (Table 1.1-1). At that time, it was difficult to distinguish between chromosomes within a given group.

Table 1.1-1. Classification of human chromosomes

Group	Size	Centromere location	Chromosomes
A	Large	metacentric (middle)	1, 2 and 3
B	Large	submetacentric (near the middle)	4 and 5
C	Medium	submetacentric	6 through 12, and X
D	Medium	acrocentric (near the end)	13, 14 and 15
E	Short	submetacentric	16, 17 and 18
F	Short	metacentric	19 and 20
G	Short	acrocentric	21, 22 and Y

Nearly 100 years earlier, John Langdon Down classified types of mental retardation based on the similarity of their looks to a ‘great division of the human race’, rather than ‘the class from which they have sprung.(Down, 1866). One of these groups was identified as Mongolian (or ‘mongols’), while other groups were termed Ethiopian or Malay. The cause of ‘mongolism’ had still not been identified by the 1950s, but was thought to possibly be a single gene defect. A French geneticist, Jerome Lejeune, observed that mongolism nearly always affected both identical twins, but rarely affected both fraternal twins (editorial, (Hulten, 1994). This inheritance pattern was not consistent with a single gene defect, and Lejeune postulated that it might be an abnormality in the number of chromosomes. Subsequently, Lejeune and his colleagues published a paper (Lejeune *et al.*, 1959) documenting that, among three cases of mongolism, all had 47 chromosomes, the excess chromosome being in the G group. They were not able to determine whether it was an additional 21, 22 or Y chromosome. Later that year, Jacobs and her colleagues confirmed these findings in an additional four cases (Jacobs *et al.*, 1959), each having an additional G chromosome. They ruled out the Y chromosome, because the female cases they observed did not have clinical characteristics of

Klinefelter syndrome (already known to be caused by an extra Y chromosome in females). Several years later, the extra chromosome was shown to be the 21st and that so called 'mongolism' was the result of trisomy 21. By the 1960s, the term 'mongoloid' was changed to Down's syndrome or to Down syndrome.

Exactly one year after the article by Jacobs and colleagues on Down syndrome appeared (Jacobs *et al.*, 1959), back-to-back articles on two other autosomal trisomies were published in the *Lancet*. The first was by John Edwards and his colleagues in Oxford (Edwards *et al.*, 1960). They described a single female with:

> "an odd-shaped skull, low-set and malformed ears, a triangular mouth with receding chin, webbing of the neck, a shield-like chest, short stubby fingers and toes with short nails, webbing of toes, ventricular septal defect, mental retardation and neonatal hepatitis".

The main indication that this infant might have a chromosome abnormality was the webbed neck. Neck webbing was a common finding in Turner syndrome that was already known to be caused by missing sex chromosome (45, X). Edwards also cited three published descriptions of similar cases to establish the definition of a syndrome. They identified 47 chromosomes, the extra being in the E group. The tentative assignment was an additional 17th chromosome, or trisomy 17.

The second paper was by Klaus Patau and his colleagues describing another new chromosome abnormality (Patau *et al.*, 1960). A single female infant with multiple congenital abnormalities (cerebral defect, cleft palate, hare lip, simian creases, trigger thumbs, polydactyly, capillary haemangiomata and heart defect) whose karyotype also showed 47 chromosomes. The additional chromosome was found to be in the D group and Patau did not speculate on which it might be (13, 14 or 15). Later, it was shown to be the 13th chromosome, or trisomy 13.

Also in 1960, David Smith (a co-author with Patau on the trisomy 13 article) reported "a new autosomal trisomy syndrome" (Smith, 1960). Based on three patients, he provided an extensive description of the congenital defects and, upon analysis, found 47 chromosomes. The extra chromosome was in the E group and was identified as chromosome 18. In an addendum, Smith reported four more unrelated infants with trisomy 18 and adds:

> "Recently, Edwards and colleagues have described a trisomy syndrome that seems to be the same as the one presented above. However, these authors identified the extra chromosome as No. 17".

The question of whether this abnormality was due to an extra chromosome 17 or 18 persisted for some time. In articles from the mid 1960s, the syndrome was referred to as trisomy 17-18 (Hecht *et al.*, 1963; Weber, 1967). Regardless, this syndrome is still referred to as Edwards syndrome, rather than Smith syndrome.