reciprocal translocation, there are single breaks in each of two chromosomes, with exchange of material. A balanced reciprocal translocation between the long arm of chromosome 2 and the short arm of chromosome 5 would be written *46,XX,t(2;5)(q31;p14)*. This individual has 46 chromosomes with altered morphology of one of the chromosomes 2 and one of the chromosomes 5. Because there has been no loss of genetic material, the individual is likely to be phenotypically normal. A balanced translocation carrier, however, is at increased risk for producing abnormal gametes. For example, in the case cited earlier, a gamete containing one normal chromosome 2 and a translocated chromosome 5 may be formed. Such a gamete would be unbalanced because it would not contain the normal complement of genetic material. Subsequent fertilization by a normal gamete would lead to the formation of an abnormal (unbalanced) zygote, resulting in spontaneous abortion or birth of a malformed child. The other important pattern of translocation is called a *robertsonian translocation* (or centric fusion), a translocation between two acrocentric chromosomes. Typically the breaks occur close to the centromeres of each chromosome. Transfer of the segments then leads to one very large chromosome and one extremely small one. Usually the small product is lost (Fig. 5-18); however, because it carries only highly redundant genes (e.g., ribosomal RNA genes), this loss is compatible with a normal phenotype. Robertsonian translocation between two chromosomes is encountered in 1 in 1000 apparently normal individuals. The significance of this form of translocation also lies in the production of abnormal progeny, as discussed later with Down syndrome.

Many more numerical and structural chromosomal aberrations are described in specialized texts, and more and more abnormal karyotypes are being identified in disease. As pointed out earlier, the clinically detected chromosome disorders represent only the "tip of the iceberg." It is estimated that approximately 7.5% of all conceptions have a chromosomal abnormality, most of which are not compatible with survival or live birth. Even in live-born infants the frequency is approximately 0.5% to 1.0%. It is beyond the scope of this book to discuss most of the clinically recognizable chromosomal disorders. Hence, we focus attention on those few that are most common.

Cytogenetic Disorders Involving Autosomes

Trisomy 21 (Down Syndrome)

Down syndrome is the most common of the chromosomal disorders and is a major cause of mental retardation. In the United States the incidence in newborns is about 1 in 700. Approximately 95% of affected individuals have trisomy 21, so their chromosome count is 47. FISH with chromosome 21–specific probes reveals the extra copy of chromosome 21 in such cases (Fig. 5-19). Most others have normal chromosome numbers, but the extra chromosomal material is present as a translocation. As mentioned earlier, the most common cause of trisomy and therefore of Down syndrome is meiotic nondisjunction. The parents of such children have a normal karyotype and are normal in all respects.

Maternal age has a strong influence on the incidence of trisomy 21. It occurs once in 1550 live births in women under age 20, in contrast to 1 in 25 live births for mothers older than age 45. The correlation with maternal age suggested that most cases the meiotic nondisjunction of chromosome 21 occurs in the ovum. Indeed, studies in which DNA polymorphisms were used to trace the parental origin of chromosome 21 have revealed that in 95% of the cases with trisomy 21 the extra chromosome is of maternal origin. Although many hypotheses have been advanced, the reason for the increased susceptibility of the ovum to nondisjunction remains unknown.

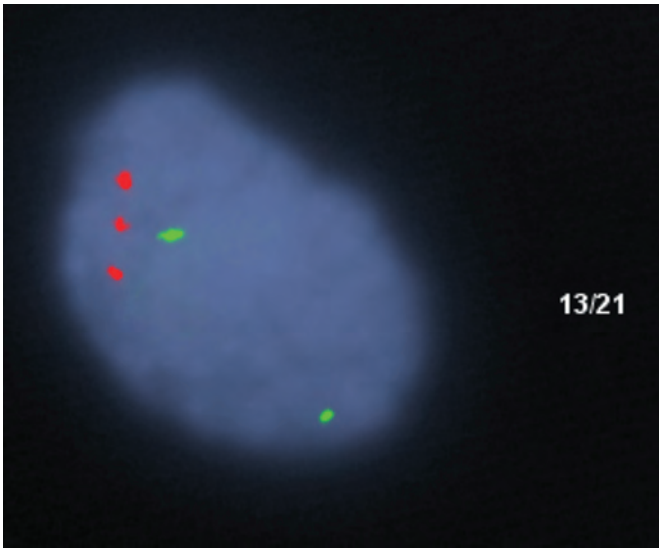

Figure 5-19 Fluorescence in situ hybridization analysis of an interphase nucleus using locus-specific probes to chromosome 13 (green) and chromosome 21 (red), revealing three red signals consistent with trisomy 21. (Courtesy of Dr. Stuart Schwartz, Department of Pathology, University of Chicago, Chicago, IL.)

In about 4% of cases of Down syndrome, the extra chromosomal material derives from the presence of a robertsonian translocation of the long arm of chromosome 21 to another acrocentric chromosome (e.g., 22 or 14). Because the fertilized ovum already possesses two normal autosomes 21, the translocated material provides the same triple gene dosage as in trisomy 21. Such cases are frequently (but not always) familial, and the translocated chromosome is inherited from one of the parents (usually the mother), who is a carrier of a robertsonian translocation, for example, a mother with karyotype 45,XX,der(14;21)(q10;q10). In cells with robertsonian translocations, the genetic material normally found on two pairs of chromosomes is distributed among only three chromosomes. This affects chromosome pairing during meiosis, and as a result the gametes have a high probability of being aneuploid.

Approximately 1% of Down syndrome patients are mosaics, having a mixture of cells with 46 or 47 chromosomes. This mosaicism results from mitotic nondisjunction of chromosome 21 during an early stage of embryogenesis. Symptoms in such cases are variable and milder, depending on the proportion of abnormal cells. Clearly, in cases of translocation or mosaic Down syndrome, maternal age is of no importance.

The diagnostic clinical features of this condition—flat facial profile, oblique palpebral fissures, and epicanthic folds (Fig. 5-20**)—are usually readily evident, even at**