birth. Down syndrome is a leading cause of severe mental retardation; approximately 80% of those afflicted have an IQ of 25 to 50. While intellectually disadvantaged, these children typically have a gentle, shy manner and often seem more content with life than their normal siblings. It should be pointed out that some mosaics with Down syndrome have mild phenotypic changes and may even have normal or near-normal intelligence. In addition to the phenotypic abnormalities and the mental retardation already noted, some other clinical features are worthy of note.

- *Approximately 40% of the patients have congenital heart disease,* most commonly defects of the endocardial cushion, including ostium primum, atrial septal defects, atrioventricular valve malformations, and ventricular septal defects. Cardiac problems are responsible for the majority of the deaths in infancy and early childhood. Several other congenital malformations, including atresias of the esophagus and small bowel, are also common.
- *Children with trisomy 21 have a 10-fold to 20-fold increased risk of developing acute leukemia.* Both acute lymphoblastic leukemias and acute myeloid leukemias occur. The latter, most commonly, is acute megakaryoblastic leukemia.
- Virtually all patients with trisomy 21 older than age 40 develop *neuropathologic changes* characteristic of Alzheimer disease, a degenerative disorder of the brain.
- Patients with Down syndrome have *abnormal immune responses that predispose them to serious infections,* particularly of the lungs, and to thyroid autoimmunity. Although several abnormalities, affecting mainly T-cell functions, have been reported, the basis of immunologic disturbances is not clear.

Despite all these problems, improved medical care has increased the longevity of individuals with trisomy 21. Currently the median age at death is 47 years (up from 25 years in 1983).

Although the karyotype and clinical features of trisomy 21 have been known for decades, little is known about the molecular basis of Down syndrome. Based on study of humans with partial trisomy of chromosome 21 and mouse models of trisomy, the critical region of human chromosome 21 that is involved in the pathogenesis has been identified. Based on these studies, several gene clusters, each of which is predicted to participate in the same biologic pathway, have been implicated. For example, 16 genes are involved in the mitochondrial energy pathway; several are likely to influence central nervous system development and one group is involved in folate metabolism. It is not known how each of these groups of genes is related to Down syndrome. The gene dosage hypothesis assumes that the phenotypic features of the trisomy 21 are related to overexpression of genes. In reality only about 37% of the genes on chromosomes 21 are overexpressed by 150%, whereas others have variable degrees of changes in expression. Further complexity in defining the specific genes involved in the pathogenesis of Down syndrome is related to the presence of several miRNA genes on chromosome 21 that can shut down translation of genes that map elsewhere in the genome. Thus, despite the availability of the gene map of chromosome 21, the progress in understanding the molecular basis of Down syndrome remains slow.

Much progress is being made in the molecular diagnosis of Down syndrome prenatally. Approximately 5% to 10% of the total cell free DNA in maternal blood is derived from the fetus and can be identified by polymorphic genetic markers. By using next generation sequencing the gene dosage of chromosome 21 linked genes in fetal DNA can be determined with great precision. This is emerging as a powerful noninvasive method for prenatal diagnosis of trisomy 21 as well as other trisomies.

Other Trisomies

A variety of other trisomies involving chromosomes 8, 9, 13, 18, and 22 have been described. Only trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) are common enough to merit brief mention here. As noted in Figure 5-20, they share several karyotypic and clinical features with trisomy 21. Thus, most cases result from meiotic nondisjunction and therefore carry a complete extra copy of chromosome 13 or 18. As in Down syndrome, an association with increased maternal age is also noted. In contrast to trisomy 21, however, the malformations are much more severe and wide ranging. As a result, only rarely do infants survive beyond the first year of life. Most succumb within a few weeks to months.

Chromosome 22q11.2 Deletion Syndrome

Chromosome 22q11.2 deletion syndrome encompasses a spectrum of disorders that result from a small deletion of band q11.2 on the long arm of chromosome 22. The syndrome is fairly common, occurring in as many as 1 in 4000 births, but it is often missed because of variable clinical features. These include *congenital heart defects, abnormalities of the palate, facial dysmorphism, developmental delay, and variable degrees of T-cell immunodeficiency and hypocalcemia.* Previously, these clinical features were considered to represent two different disorders—*DiGeorge syndrome* and *velocardiofacial syndrome*.

Patients with DiGeorge syndrome have thymic hypoplasia, with resultant T-cell immunodeficiency (Chapter 6), parathyroid hypoplasia giving rise to hypocalcemia, a variety of cardiac malformations affecting the outflow tract, and mild facial anomalies. The clinical features of the so-called velocardiofacial syndrome include facial dysmorphism (prominent nose, retrognathia), cleft palate, cardiovascular anomalies, and learning disabilities. Less frequently, these patients also have immunodeficiency.

Until recently the overlapping clinical features of these two conditions (e.g., cardiac malformations, facial dysmorphology) were not appreciated; it was only after these two apparently unrelated syndromes were found to be associated with a similar cytogenetic abnormality that the clinical overlap came into focus. Recent studies indicate that, in addition to the numerous structural malformations, individuals with the 22q11.2 deletion syndrome are at a particularly high risk for psychotic illnesses, such as *schizophrenia and bipolar disorders. In fact, it is estimated that schizophrenia develops in approximately 25% of adults with this syndrome.* Conversely, deletions of the region can be found in 2% to 3% of individuals with childhood-onset schizophrenia. In addition, attention deficit hyperactivity disorder is seen in 30% to 35% of affected children.

The diagnosis of this condition may be suspected on clinical grounds but can be established only by detection