

plication rate (about 2 percent)¹ have made it the treatment of choice for patients with frequent, symptomatic episodes.

However, the appropriate strategy for persons with asymptomatic Wolff–Parkinson–White patterns on the electrocardiogram has been controversial. Although ventricular fibrillation leading to sudden death may be the first manifestation of the Wolff–Parkinson–White syndrome, it is rare. In at least five population-based studies² in which more than 600 asymptomatic patients were followed for 5 to 20 years, only two sudden deaths overall were recorded. As a result, the pendulum swung from initial concern about the need to develop aggressive treatment strategies for asymptomatic patients to a consensus that electrophysiological evaluation and ablation should not be recommended for such patients. Exceptions have been made for patients who have high-risk occupations, such as airline pilots and firefighters. The risk of a fatal arrhythmia must be weighed against the risk of death due to ablation (approximately 0.1 percent).^{1,3}

In a prospective study reported in this issue of the *Journal*, Pappone and colleagues (pages 1803–1811) randomly assigned asymptomatic “high-risk” patients (patients ≤ 35 years of age in whom arrhythmias were inducible during electrophysiological study) to undergo ablation or to receive no therapy. The patients who underwent ablation had significantly fewer symptomatic episodes during follow-up. In one high-risk, asymptomatic patient who was randomly assigned to the control group, ventricular fibrillation subsequently developed. It is important to note that the development of symptomatic episodes due to atrioventricular reciprocating tachy-

cardia is not the same as sudden death. Moreover, markers of high risk remain controversial. Certainly, the delineation of genetic factors underlying the pathogenesis of the Wolff–Parkinson–White syndrome or malignant responses to stochastic environmental stressors that may precipitate symptomatic arrhythmias, sudden death, or both would contribute to our clinical armamentarium. However, genetic causes have thus far been identified only for rare, complex forms of the Wolff–Parkinson–White syndrome that include hypertrophic cardiomyopathy or glycogen storage disease,^{4,5} and even in these unusual cases, the genetic causes have not yet been correlated with outcomes. Whether prophylactic ablation for the prevention of symptomatic episodes will gain wide acceptance remains to be seen. What is certain is that these new data will animate debate on a critical question that was thought to have been put to rest.

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Have We Seen the Last Variant of Severe Combined Immunodeficiency?

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Over the past 15 years, deciphering of the molecular defects in primary immunodeficiencies has spawned a stream of information on how the immune system works. These advances have been facilitated by the development of powerful new tools that make possible the analysis of the genome and

genetic errors. During this time of advances in knowledge of basic immunology, we have also improved medical services for patients with genetically disabled immune systems. Today, accurate diagnosis, precision in prognostication, sophisticated genetic counseling, and new treatments have im-

proved and extended the lives of countless children with inherited immunodeficiency diseases.

One of the most intensively studied classes of congenital immunodeficiency diseases is severe combined immunodeficiency (SCID). There are multiple variants of SCID, but all of them involve a block in T-cell differentiation, which usually requires urgent therapy with allogeneic hematopoietic stem-cell transplantation to provide the missing progenitors of T cells. In this issue of the *Journal* (pages 1821–1828), Dadi et al. describe a new form of SCID, CD3 δ deficiency. In this variant, there is a selective block in the differentiation of lymphocytes: the development of T cells is completely arrested, whereas the differentiation of other subgroups of lymphocytes — natural killer cells and B cells — and other hematopoietic lineages appears to be normal. That two of the three affected infants in the kindred described by Dadi et al. died from viral infections before four months of age is a striking demonstration of the essential role of T cells in the defense against viruses, even weakly pathogenic adenoviruses and cytomegalovirus.

Nine different molecular defects are known to cause SCID. These nine genetic variants engender four distinct phenotypes. Adenosine deaminase (ADA) deficiency (accounting for 10 to 20 percent of cases of SCID) allows toxic amounts of deoxyadenosine to accumulate in progenitors of lymphocytes and, ultimately, kill the precursors of T cells, B cells, and natural killer cells (see Figure). The absence of both T cells and natural killer cells is the consequence of mutations in either the gene encoding the γ c subunit of receptors for several growth-promoting cytokines (X-linked SCID, accounting for 50 percent of cases) or the gene for the allied Janus kinase 3 (accounting for 5 to 10 percent of cases).

An impairment of genes responsible for somatic rearrangements of the V, D, and J elements of the T-cell and B-cell receptors also causes faulty development of T and B cells (see Figure). The mutations behind this variant of SCID affect three genes that encode proteins of the recombination machinery: the recombination activating gene 1 or 2 (accounting for 10 percent of cases) or *Artemis* (accounting for 10 percent of cases).

Finally, three distinct defects can cause an isolated deficiency of T cells: lack of the α chain of the interleukin-7 receptor (accounting for 5 to 10 percent of cases), deficiency of CD45 (a glycoprotein involved in T-cell signaling), and, as reported by Dadi et al., absence of CD3 δ (accounting for less than

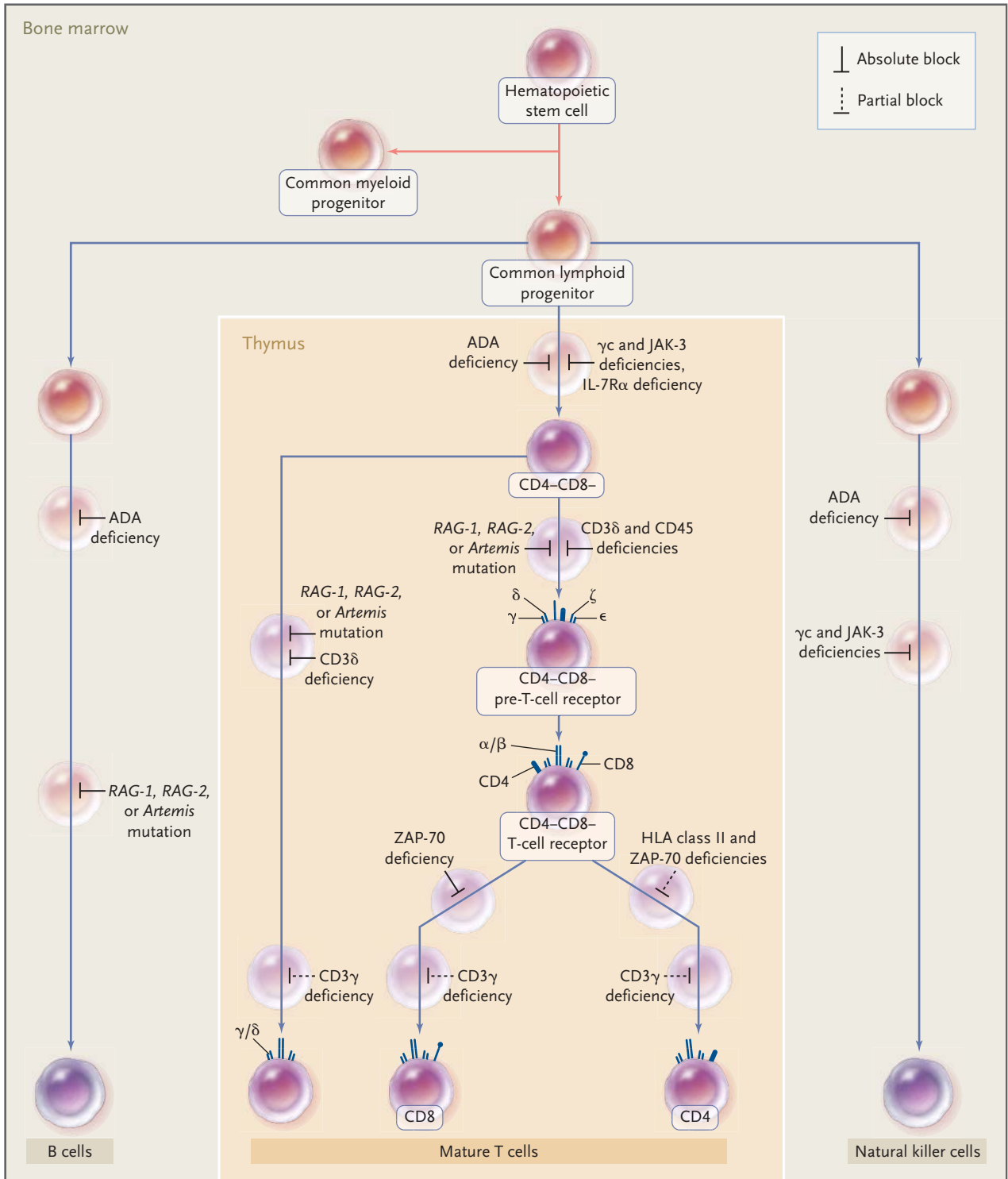
1 percent of cases) (see Figure). Is this the complete list of the molecular defects in SCID? Almost, because these known genetic defects account for over 90 percent of cases. Reticular dysgenesis (a mixed myeloid–lymphoid defect) and some selective T-cell deficiencies still escape our understanding.

CD3 δ deficiency is the first primary immunodeficiency for which oligonucleotide microarray analysis has been used to find the mutated gene. This technical tour de force was based on a comparison of the gene-expression profile in one of the patient's thymocytes with that in normal thymocytes. The results of a comparison between diseased and control tissues may, however, be misleading, because oligonucleotide microarray analysis of a heterogeneous population of cells may not detect transcripts of genes in a minor subpopulation of undifferentiated cells. Moreover, a mutation that does not im-

Figure. T-Cell Lymphopoiesis and the Main Known Molecular Deficiencies in T-Cell Development.

Hematopoietic stem cells with a capacity for self-renewal give rise to multipotent progenitors and then to putative lymphoid and myeloid common progenitors. Common lymphoid progenitors can differentiate into natural killer cells, B cells, and T cells. The pathway involved in T-cell differentiation is somewhat detailed; it includes the following steps: committed T-cell precursors differentiate first into CD4–CD8– double-negative precursors expressing the precursor T-cell receptor associated with the CD3 subunits γ , δ , ϵ , and ζ , then into CD4+CD8+ double-positive thymocytes expressing an α/β T-cell receptor associated with the CD3 subunits, and finally into mature CD4+CD8– or CD4–CD8+ single-positive T cells. The γ/δ T-cell receptor pathway branches off from the CD4–CD8– thymocytes.

The representation of the CD3 subunit does not reflect its stoichiometry, which is γ , δ , ϵ 2, ζ 2. An absolute or a partial block at the points indicated has been observed in the following T-cell immunodeficiencies: adenosine deaminase (ADA) deficiency, which induces premature apoptosis of lymphoid precursors; deficiencies of the γ chain (γ c) and Janus kinase 3 (JAK-3), which cause defects in γ c-dependent signaling; deficiency of the α chain of the interleukin-7 receptor (IL-7R α), which causes a defect in signaling through interleukin-7; somatic rearrangements of the V, D, and J elements caused by mutations in recombination activating gene 1 or 2 (*RAG-1* and *RAG-2*, respectively) or in the *Artemis* gene, which impairs the generation of T-cell (and B-cell) receptors; CD3 δ deficiency; CD45 deficiency; deficiency in the expression of HLA class II molecules; zeta-associated protein 70 (ZAP-70) deficiency; and CD3 γ deficiency. The exact position of the developmental blocks causing ADA, JAK-3, IL-7R α , and CD45 deficiencies has largely been deduced from experimental data in knockout mice.



pair the synthesis and stability of the corresponding messenger RNA can be overlooked. Given the consanguinity in the kindred of the three patients with CD3 δ deficiency, analysis of the segregation of polymorphic markers (e.g., single-nucleotide polymorphisms) would have allowed assignment of the disease locus to the 11q23 region where the CD3 δ gene lies. Such a linkage analysis might have been a simpler way of tracking down the mutant gene.

The identification of CD3 δ deficiency was aided by the surprising radiographic finding of a thymic shadow in a patient with SCID and the long-standing experience and skill of the Toronto team in performing thymus biopsies in immunodeficient children. Such a biopsy, strictly a research procedure, provided tissue that showed that CD3 δ deficiency is associated with a block at the stage of expression of the precursor T-cell receptor (see Figure).

The four subunits of CD3 — γ , δ , ϵ , and ζ — associate with the T-cell receptor and transmit activating signals into the T cell when its receptor binds to an antigen. These four subunits also form

a complex with the precursor T-cell receptor, which consists of the T-cell receptor β chain and the precursor T-cell receptor (see Figure). The presence of CD3 δ in this complex is essential for the differentiation of T-cell precursors to proceed.

It has long been suspected that the four CD3 subunits have distinct roles — a concept supported by the consequences of CD3 δ deficiency as compared with the clinical repercussions of CD3 γ deficiency. The first causes a complete block in T-cell differentiation, whereas disabling mutations of CD3 γ cause a milder immunodeficiency in which patients have slightly reduced numbers of T cells and low but detectable amounts of the CD3–T-cell receptor complex on the surface of T cells. All these molecular and genetic studies of SCID illustrate how useful the analysis of natural mutants can be in elucidating the development of the immune system, provided that one keeps in mind the obvious limitations in studies of human physiopathology.

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