primary care clinicians, increase the flow of providers to rural areas, strengthen and support rural health care institutions, and integrate rural health care into larger regional systems.

Although they may live at the geographic periphery, rural patients increasingly demand access to the same spectrum and quality of care as their urban counterparts. Improving the quality of rural health care requires the integration of providers and institutions into larger systems, through the creation of networks and the use of electronic health records and telemedicine. Many complex services cannot be supplied safely or at a reasonable cost in rural communities. Effective rural systems must be based on a menu of core services, delivered largely by generalists in stable hospital and outpatient settings that are linked to regional centers.

Ensuring stability is a challenge. Because of the small size of many rural delivery systems, the loss of a hospital or a provider can undermine an entire local system. Congress has temporarily created an island of fiscal equilibrium for smaller rural hospitals through the Critical Access Hospital program. No such national policy has emerged with regard to the health care workforce. Because medical and nursing programs are dominated by academic health centers with relatively little experience or interest in rural medicine, training has not met national needs. If we are to maintain high-quality patient care in rural communities, we need to develop mechanisms to attract and retain clinicians who are willing to practice in rural settings. Rural health care systems — because of their size and geography — will always be somewhat fragile. But a concerted national policy to sustain strong rural health care institutions — and the personnel to staff them — can ensure that access to and quality of care do not lag behind those in urban areas.

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Factor VIII, d-Dimer, and Thromboembolism in Children
Ulrike Nowak-Göttl, M.D., and Andrea Kosch, M.D.

Symptomatic venous and arterial thromboses are being diagnosed with increasing frequency in neonates, infants, and children. Because of the special properties of the hemostatic system in children, thrombotic manifestations are not rare in the pediatric population: they occur in 0.07 of every 10,000 children and account for 5.3 of every 10,000 pediatric hospital admissions and 2.4 of every 1000 admissions of newborns to intensive care units. Perhaps the lower concentrations of physiological inhibitors of the coagulation system, along with more limited fibrinolytic capacity, account for the greater
risk of thromboembolic complications among neonates than among older children. The incidence of such vascular accidents decreases substantially after the first year of life, with a second peak during puberty and adolescence, again associated with reduced fibrinolytic activity.¹

A broad range of clinical and environmental conditions can provoke an increase in the generation of thrombin, with subsequent thrombus formation. These include postpartum asphyxia, infections in neonates, fetal diabetes, the use of central venous cannulation, trauma or surgery, dehydration, cancer, renal diseases, autoimmune diseases, obesity, immobilization, and the use of oral contraceptives by adolescent girls. In addition, various genetic prothrombotic defects, particularly those affecting the physiological anticoagulant systems (deficiency of antithrombin, protein C, or protein S), the G1691A mutation of coagulation factor V, and the prothrombin G20210A gene variant, are risk factors for thrombotic events in white people. Homocystinuria, moderate hyperhomocysteinemia, and increased concentrations of lipoprotein(a) have recently been shown to increase the risk of thromboembolic arterial or venous thrombosis in children and adults. Furthermore, the Leiden Thrombophilia Study has underlined positive associations between the risk of venous thrombosis and high levels of factor VIII, factor IX, factor X, and thrombin-activatable fibrinolysis inhibitor and low levels of tissue-factor-pathway inhibitor.

However, 30 to 40 percent of patients with symptomatic thromboembolism have no identifiable inherited prothrombotic risk factors. For this reason, studies of hemostatic factors in relation to the onset and recurrence of thrombosis could be revealing. The fibrin fragment in plasma called D-dimer is a marker of fibrin formation and reactive fibrinolysis, and D-dimer levels are elevated during acute thromboembolic episodes. Possibly because of the additive effects of multiple genetic and nongenetic procoagulant factors, elevated D-dimer levels have been found in patients with subclinical atherosclerosis or coagulation disorders that confer a predisposition to coronary thrombosis and in adults with recurrent venous thromboses.² The concept that symptomatic thromboembolism is not a single disease but a multifactorial disorder has led to the understanding that the association of multiple prothrombotic defects, or the combination of established prothrombotic risk factors with environmental or clinical conditions, greatly increases the risk of new and recurrent thrombosis — not only in adults, but also in infants and children (see Figure).

In contrast to the many published reports concerning thromboembolism in adults, only sparse data are available from long-term follow-up and outcome studies in children with venous or arterial thromboembolism. In this issue of the Journal, Goldenberg et al. (pages 1081–1088) report data that contribute to the understanding of venous thromboembolic diseases in children. In a prospective survey, they found persistently elevated concentrations of factor VIII, D-dimer, or both after a standard antithrombotic treatment regimen lasting for at least three to six months in children who had a poor outcome, defined as persistence of the thrombus, occurrence of the post-thrombotic syndrome, or recurrence of a thrombus. Confirming the previous findings in adults with symptomatic venous thromboembolism, the data reported by Goldenberg et al. indicate that a plasma factor VIII level of more than 150 IU per deciliter and a plasma D-dimer level of more than 500 ng per milliliter, separately or together, are significant and independent risk factors for a poor outcome in children with thrombosis. Elevated factor VIII levels, D-dimer levels, or both early in the course of the disease were highly predictive of a poor outcome; if the levels were elevated at diagnosis, the odds ratio for a poor outcome was 6.1; the odds ratio was 4.7 in cases in

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**Figure.** Cumulative Recurrence-free Survival among 301 White German Children with Idiopathic Deep Venous Thrombosis.

The recurrence-free survival after the discontinuation of standardized anticoagulant–antithrombotic therapy (lasting for six months) was significantly reduced among carriers of two or more genetic risk factors.
which at least one of the two laboratory abnormalities persisted at three to six months of follow-up. After that time, there was no change in outcomes throughout the remaining two-year study period.

The findings of this study, involving a cohort of 82 children ranging in age from newborn to 20 years (median, 12 years) for whom complete laboratory and clinical follow-up data were available, cannot necessarily be generalized to other children. The 51 percent rate of poor outcomes in this prospectively studied cohort (with a median follow-up of 12 months) represents the tip of the iceberg for neonates, toddlers, and preschool-age children; the actual incidence of poor outcomes will become apparent within the next 5 to 15 years, when the majority of the younger children enrolled in the study have passed puberty.

The hypothesis that symptomatic thromboembolism is a multifactorial disorder rather than a uniform disease prompts us to recommend further studies to clarify the role of elevated factor VIII and d-dimer levels and their interaction with inherited or acquired prothrombotic conditions in pediatric populations of different ethnic backgrounds. Since factor VIII levels not only are assay-dependent and age-dependent, but also vary among ABO blood groups (which are associated with levels of von Willebrand factor), individual cutoff values will have to be defined for different populations of neonates, infants, and children.

Prospective studies of thromboembolism in children such as that reported by Goldenberg et al. are of major importance in the effort to stratify risk for individual patients, because they will guide anticoagulant and antithrombotic treatment in children with thrombosis in such a way as to optimize prevention and minimize the risk of complications. Children with thrombosis are not small adults, and the treatment protocols for adults cannot automatically be scaled down to generate the appropriate regimens for children. For this reason, and to improve future prospective trials of anticoagulant and antithrombotic treatment in children, a consensus of experts concerning standardized measurements of clinical outcome, imaging methods, and follow-up intervals for children with thrombosis is urgently required. The prevention of thrombosis-related complications in children will considerably reduce the burden of the disease and its associated costs.

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Drugs and the QT Interval — Caveat Doctor
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All drugs have the potential to cause adverse effects. Occasionally, serious adverse effects are not identified in preclinical studies and become apparent only when a drug is in widespread clinical use — a particular problem with adverse events that are rare and result in few symptoms. One example of relevance to clinicians and regulatory agencies is drug-induced prolongation of the QT interval. During the past few years, many drugs have been removed from the market or required to include “black box” warnings on their labels because of the potential for QT-interval prolongation. The list of causative medications is daunting, and the number and variety of interactions involving these drugs can seem overwhelming.

After adjustment for the heart rate, the corrected QT interval is considered to be prolonged if it is more than 450 msec in men or more than 460 msec in women (see Figure). This prolongation most often results from delayed ventricular repolarization, a process that is mediated by the efflux of intracellular potassium. The channels responsible for this current are susceptible to blockade by many drugs, producing a suitable environment for the development of torsades de pointes, a polymorphic form of ventricular tachycardia that is characterized by the twisting of the QRS axis around the baseline. Although it is often self-terminating, torsades de pointes can sometimes lead to sudden death.

Non–drug-related factors associated with pro-