After more than a century of effort, atherosclerosis research has finally, in the last 10 years or so, progressed from understanding pathogenesis to establishment of successful treatments. Dietary intervention with oily fish, daily ingestion of aspirin, as antiplatelet therapy, and latterly cholesterol lowering have provided significant reduction of risk of subsequent coronary events, including unstable angina and myocardial infarction. The trial evidence is now so convincing, as is being reviewed by Rabbani and Topol [1], that the debate has moved on from “whether to treat” to “whom to treat”, a judgement based on health economic considerations influenced by the balance of benefits and risks. One of the challenges for health planners is that the benefits of these interventions, while highly significant, are arguably modest, amounting to a 50% or so overall risk reduction [1]. Moreover, the reduction in risk is spread evenly over high and low risk groups, which implies the need to treat many healthy individuals to prevent each clinical event. One response to this situation would be to hope that, as statins become generic drugs, treatments will become inexpensive enough to apply on a population-wide basis. A second more exciting and dynamic approach is to build on the “proof of principle” provided by the existing trial successes to develop more targeted and effective treatments. This latter approach provides the backdrop to this focussed issue. There is emerging consensus that plaque instability rather than progression should be the proper target for new therapies, because it is instability that underlies most clinical events (see for review Gutstein and Fuster [2]). The pathological features associated with plaque instability, namely a thin fibrous cap, large lipid pool and the preponderance within plaques of inflammatory cells over smooth muscle cells and collagen matrix are described by van der Wal and Becker [3]. The biological factors, prominently inflammation and matrix degradation, and biomechanical factors, prominently locally increased wall stress, that underlie the association of these pathological features with the final rupture event are discussed by Arroyo and Lee [4]. Several articles then expand on important individual facets of the morphogenesis of stable and unstable plaques, which include vascular smooth muscle cell proliferation, migration and matrix formation (Newby and Zaltsman [5]), apoptosis of smooth muscle cells (Bennett [6]), collagen synthesis (Rekhter [7]) and the role of intercellular adhesion molecules expressed on smooth muscle cells (Braun et al. [8]). A consensus emerges that these processes are in delicate balance and have potentially opposing roles in plaque progression and destabilisation. Siow et al. [9] contribute a provocative article proposing a hitherto unappreciated role for the heme oxygenase-carbon monoxide pathway in atherogenesis. Finally, Bates and Weitz [10] consider what new therapeutic possibilities exist for modulating thrombus formation on unstable plaques and hence preventing progression to the clinically overt syndromes of unstable angina and myocardial infarction. Original articles encompass new data regarding local arterial wall remodeling (Smits et al. [11]) the role of plaque microvasculature (de Boer et al. [12]), smooth muscle proliferation (Lutgens et al. [13]), and apoptosis (Bauriedel et al. [14]) therein. The specific role of genes, overexpressed in plaques, such as nitric oxide synthase (Depre et al. [15]) and 12-lipoxygenase (Natarajan et al. [16]) is also considered. New insights into collagen induced platelet aggregation are presented by Knight et al. [17] and a new approach to reducing restenosis after angioplasty and stenting is described by Stefanadis et al. [18]. We believe that this collection of
reviews not only provides a consensus of current knowledge but also sets out an agenda for future research leading to rationally-based therapy. The original articles illustrate the potential for advance. We offer this focussed issue as a guide to stimulate progress in the coming decade.

References