bleeding by promoting fibrinolysis as platelets are activated and release their contents at sites of clot formation.

In this issue, Kufrin and colleagues (page 926) have shed light on this interesting platelet disorder by generating transgenic mice with platelet-specific u-PA overexpression. As with QPD patients, transgenic mice exhibited a bleeding diathesis that was corrected with orally administered fibrinolysis inhibitors. Lysates of transgenic platelets rapidly degraded factor V. Platelet von Willebrand factor and fibrinogen were degraded in transgenic mice, while there was no evidence of a fibrinolytic state in plasma. Platelet-specific u-PA expression protected mice against thrombosis, and transfusion experiments revealed that overexpression of u-PA within only a minor population of the total pool of circulating platelets was sufficient to confer an antithrombotic effect.

These detailed studies demonstrate that platelet-specific overexpression of u-PA recapitulates the phenotype of QPD and suggest that the abnormal bleeding in this disorder may result predominantly from u-PA-induced hyperfibrinolysis within the environment of the hemostatic plug, as opposed to proteolytic degradation of platelet alpha-granule components. The studies by Kufrin and colleagues also support the intriguing potential of targeting expression of fibrinolytic and hemostatic proteins to the platelet alpha-granule as a strategy to treat thrombotic and bleeding disorders.

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Peptide decoys: cure for FVIII inhibitors?

Hemophilia A is a genetic disorder characterized by a deficient factor VIII (FVIII) activity. Among patients receiving FVIII replacement therapy, a significant number develop antibodies inhibiting FVIII procoagulant activity (called inhibitors). Development of inhibitors severely complicates the course of the disease, dramatically decreasing the efficacy of FVIII replacement therapy. The problem of inhibitors is one of the most complex in hemophilia A treatment, because a great variety of inhibitors directed against different epitopes in the FVIII molecule is found in individual patients. At present, there is no effective solution for this problem, and any developments in this area are greatly appreciated by clinicians.

The novel study by Villard and colleagues in this issue (page 949) appears promising, as it demonstrates that peptide surrogates, mimicking epitopes recognized by inhibitors, may block their inhibitory activity, thereby allowing restoration of a normal procoagulant activity of FVIII. To prove their concept, Villard et al used the human monoclonal inhibitory antibody Bo2C11 specific for the C2 domain of FVIII as a model for inhibitors. The authors showed that selected dodecapeptides neutralized the Bo2C11 inhibitory activity in the functional test. Moreover, these peptides were efficient in preventing inhibition of FVIII activity by Bo2C11 in a murine FVIII-knockout model of hemophilia A, suggesting that peptide decoys may also be used in vivo. Remarkably, the phage display technology used by the authors allowed selection of peptides that lack sequence homology with FVIII and therefore do not interfere with FVIII function.

But a number of issues should be addressed in order to evaluate the potential of peptide decoys for hemophilia A treatment: peptide half-life in vivo should be improved; the polyclonal nature of inhibitors and differences in inhibitors spectra among patients require designing mixtures of peptides which mimic different FVIII epitopes. In summary, the study of Villard et al outlines a novel approach to the solution of inhibitor problems in hemophilia A.

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Radicals accused of causing MALT lymphomas

Cancer in an inflammatory context is an old conundrum. We have accepted the existence of viruses that, in the long run, can cause cancer, and we believe in the association between bilharziosis and cancer of the urinary bladder. It was, however, slightly irritating for many of us to learn that *Helicobacter pylori* gastritis and an increased rate of gastric malignancies, especially gastric B-cell lymphomas, is not just an epidemiologic association. This ancient, parasitic micro-organism, already dwelling in the stomachs of human infants and, way down the evolutionary tree, of sharks, is indeed a causative agent, as evidenced by lymphoma regression following antibiotic treatment. With researchers extending this fascinating insight into lymphomagenesis, data have been generated by many independent labs converging in the current concept that, in chronic *H pylori* gastritis, an incremental, initially T-cell-dependent B-cell clonality develops. The first clear-cut evidence that this clonality actually denotes cancer is the emergence of genomic aberrations. In gastric mucosa-associated lymphoid tissue (MALT) lymphomas, at least 3 early genomic events have been described: trisomy 3 (Wotherspoon et al, Blood. 1995; 85:2000-2004) and the translocations t(11; 18)(q21;q21) (Ott et al, Cancer Res. 1997; 57:3944-3948.) and t(1;14)(p22;q32) (Willis et al, Cell. 1999;96:35-45; Zhang et al, Nat Genet. 1999;22:63-68). These 3 structural chromosomal aberrations, although all leading to the histology currently classified as extranodal marginal zone lymphoma (MZL) of MALT could be considered as different diseases. t(11;18)(q21;q21) seems to protect from further malignant progression, as is observed in non-t(11;18)(q21; q21) MZLs of MALT, and may be less sensitive to *H pylori* eradication. MZLs with t(11;18)(q21;q21) or t(1;14)(p22;q32), although involving differently rearranged genes, may converge in a common pathogenic pathway leading to abnormal activation of NF-κB (Lucas et al, J Biol Chem. 2001;276:19012-19019).

This scenario becomes even more complex against the background of 2 reports published in this issue. Ye and colleagues

(page 1012) have found an association between t(11;18)(q21;q21) of gastric MALT lymphomas and CagA strains of *H pylori.* Furthermore, they show that t(11;18)(q21;q21)-positive MZLs of MALT in other sites do occur, however, in a nonrandom fashion (ie, 38% and 24% in the lung and stomach, respectively, versus 1% in the salivary gland). Ye et al's proposal that the missing link might be chromosomal damage caused by oxidative stress induced by coinfiltrating neutrophils is intriguing. All the more so since this hypothesis is supported by data from Rollinson and colleagues (page 1007). Fascinatingly, using a completely different line of argument, these authors arrive at the very same conclusion. They show that, in their series of gastric MZLs, the glutathione *S-transferase GST T1 null* genotype and the *Interleukin-1 RN2/2* genotype, but not the *GST M1 null* genotype or *Interleukin-1 RN1/1* genotype, are associated with gastric MZLs. Thus, interindividual variations in inflammatory responses and differences in antioxidative capacity may be the genetic background on which *H pylori* can eventually exert its oncogenic potential. At this stage, it is certainly very important to investigate whether this interindividual variation of inflammatory response might even lead to a specific genetically defined subset of MZLs.

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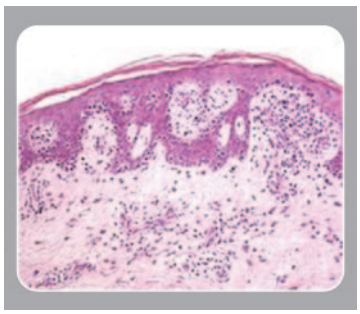
A profile of mycosis fungoides

Mycosis fungoides is the most common primary lymphoproliferative disorder of skin. The disease may be difficult to diagnose, particularly in the early patch and plaque stages, when it may resemble a chronic inflammatory dermatitis. The neoplastic cells of mycosis fungoides are $CD3^+$ T cells, which are usually $CD4^+$ T helper cells, and may or may not exhibit an aberrant immunophenotype, with loss of CD7 expression. A number of nonneoplastic conditions, including inflammatory dermatoses, may exhibit an identical immunophenotype, adding to the difficulty of early diagnosis. Often, the diagnosis becomes evident only after multiple biopsies, over a period of months to years. With disease progression, increasing epidermotropism and cytologic atypia are seen, allowing for more definitive diagnosis. With advanced-stage disease, skin tumors may form and neoplastic cells may spread to extracutaneous sites. The pathogenesis of mycosis fungoides is unknown.

In this issue, Tracey and colleagues (page 1042) apply gene-expression profiling techniques to mycosis fungoides, an approach that should significantly expand our knowledge of the disease. First, they identify a 27-gene expression signature, using cDNA microarray analysis on 29 cases of mycosis fungoides and 11 cases of inflammatory dermatoses, which distinguishes between the two. From this they extract a set of 6 genes whose expression can discriminate between mycosis fungoides and inflammatory conditions in 97% of cases. The set of 27 mycosis fungoides–expressed genes, which includes a number of genes involved in the regulation of signaling by tumor necrosis factor (TNF), may hold clues to the pathogenesis of the disease. Finally, through hierarchical clustering of the gene expression data, the authors define 2 main groups of mycosis fungoides cases, one of which includes those that are more aggressive, including cases with tumor-stage disease.

Gene-expression analysis by microarray techniques has been utilized to refine tumor classification for a number of malignant neoplasms, including large B-cell non-Hodgkin lymphoma and breast carcinoma.



Tracey and colleagues have now applied this method to a T-cell lymphoma, providing us with a new set of markers that may aid in disease diagnosis, as well as providing a preliminary gene-expression-based tumor classification scheme for mycosis fungoides. Future gene-expression profiling studies, to compare mycosis fungoides with the related Sézary syndrome, other T-cell lymphomas, and benign mimics, such as pseudolymphomatoid drug eruption, will further advance this diagnostically challenging field.

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Prognostic staging in myeloma: in search of biology

For 30 years, clinicians relied on the Durie-Salmon staging system (Durie and Salmon, Cancer. 1975;36:842-854) to define risk in multiple myeloma (MM). In recent years the β_2-microglobulin (β_2M) and C-reactive protein (CRP) have added to the prognostic arsenal (Bataille et al, Blood. 1992;80:733-737). Despite their longevity, both staging systems are limited by an inability to segregate risk accurately in all cases, a particular problem in such a heterogeneous disease. Indeed, until recently prognostic prediction has been something of an irrelevance since all patients with symptomatic disease received essentially the same therapy. Lately, however, the landscape has changed and identification of accurate prognostic biomarkers has assumed increasing importance since therapeutic options may now vary widely according to disease biology.

In this issue, Terpos and colleagues (page 1064) take a step in this direction by examining the roles of the receptor activator of nuclear factor κB ligand (RANKL) and RANK/osteoprotegerin (OPG), which play a dominant role in osteoclast activation and probably in the bone disease common to MM patients (Mundy, Nat Rev Cancer. 2002;2:584-593). The authors demonstrate