Clinical and Immunological Aspects of Wegener's Granulomatosis (WG) and other syndromes resembling WG*

Peter Lamprecht MD, Andreas Trabandt MD and Wolfgang L. Gross MD

Department of Rheumatology, University of Lobeck, and Rheumaklinik Bad Bramstedt, Germany

Key words: Wegener's granulomatosis, initial phase, generalized phase, Th1/Th2 cytokine profile

IMAJ 2000;2:621–626

Wegener's granulomatosis was defined by the Chapel Hill Consensus Conference as an anti-neutrophil cytoplasmic antibody-associated, pauci-immune, primary systemic vasculitis affecting predominantly small vessels (i.e., arterioles, capillaries and venules). This definition implicates the presence of two distinct features in the disease. One is the detection of ANCA in the serum, and the other is the absence or paucity of immune complex deposits in areas of vasculitis in immunohistochemical studies of tissue specimen. Granulomatous inflammation involving the respiratory tract and frequent association with necrotizing glomerulonephritis are also part of the definition of Wegener's granulomatosis. The initiating agent(s) is/are still unknown. Thus, the vasculitis in the disease is coined "primary" [1]. The American College of Rheumatology criteria distinguish patients with WG from other patients with a different vasculitis on the basis of criteria with high level sensitivity and specificity. The four criteria for WG include abnormal urinary sediment, abnormal findings on chest X-ray, oral ulcers or nasal discharge, and granulomatous inflammation on biopsy. The presence of two or more of these four criteria are associated with a sensitivity of 88.2% and a specificity of 92.0% [2]. However, neither the Chapel Hill Consensus nomenclature and definitions of primary systemic vasculitides nor the ACR classification criteria can be taken as diagnostic criteria. Neither addresses the problem of variants of the disease [3]. Immunopathogenetic aspects other than the ANCA association and paucity of immune complexes in biopsies of WG have not reached maturity or consensus to be included into the disease definition or even diagnostic criteria [4]. Nonetheless, careful observation of the clinical presentation of "classic" WG and variants and a thorough work-up of immunopathogenetic aspects of WG will lead to new pathogenetic insights, diagnostic tools and therapeutic options, as shall be discussed in this review.

Clinical features

Clinical features of the disease include "classic" presentation with an initial phase and subsequent generalization and variations of this pattern. Other diseases may mimic Wegener's granulomatosis. Furthermore, there may be true cases of granulomatous disease with features of two entities. These presentations are discussed in the following six sections.

"Classic" Wegener's granulomatosis

"Classic" WG takes a biphasic disease course, beginning with an initial phase and followed by subsequent generalization of the disease. The initial phase is characterized by granulomatous inflammation of the respiratory tract. Nasal obstruction, bloody nasal discharge or frank epistaxis, crusting, mucosal ulcerations, hoarseness, chronic sinusitis, otitis media and mastoiditis are frequently found. Saddle nose deformity, septum perforation and inspiratory stridor due to subglottic tracheal stenosis may evolve at later stages [5]. Lower respiratory tract involvement in initial-phase WG is usually restricted to ulcerating tracheobronchitis, bronchus stenoses and granulomas. Initial-phase WG may sometimes take the form of isolated lung granulomas, making it difficult for a differential diagnosis to other granulomatous inflammatory diseases of the lung, e.g., necrotizing sarcoid granulomas [6]. The disease course may be complicated by cavitation of lung nodules, and spreading of granulomatous masses per continuitatem into the oral cavity, retrobulbar space and through locations of minor resistance, such as the lamina cribrosa, into the meninges and cerebrum [3,5].

Generalization of WG is encountered after a variable time ranging from weeks to years. The evolution of the two phases, i.e., initial and generalized, cannot always be distinguished from each other, thus not permitting a clear-cut delineation of a biphasic course. Generalization often takes a fulminant course. WG may also start as "pure" small vessel vasculitis in the absence of obvious granulomatous lesions [5]. Generalization is heralded by constitutional symptoms such as malaise, fever, night sweats and weight loss. Polymyalgia, arthralgia and/or arthritis are seen in more than two-thirds of patients. Myositis and periostitis are rare musculoskeletal manifestations of WG [7]. Secondary relapsing polychondritis is seen in some patients [8]. New constitutional symptoms and/or rheumatic complaints are a sign of impending generalization or relapse. These symptoms require delimitation from accompanying infections. ANCA positivity is found in 50%

* See also case report by Codish et al., page 630–631
ANCA = anti-neutrophil cytoplasmic antibodies
WG = Wegener's granulomatosis
ACR = American College of Rheumatology

of the patients in initial-phase WG, whereas proteinase 3-ANCA positivity will be seen in up to 95% of patients with generalized WG [3]. The typical aspect of full-blown generalized WG is the pulmonary-renal syndrome. Renal involvement may range from asymptomatic microhematuria to rapidly progressive necrotizing glomerulonephritis with renal failure within days [9]. Pulmonary involvement may vary and ranges from asymptomatic pulmonary infiltrations including nodules with persistent cough, dyspnea, to bland hemoptysis and ultimately to the alveolar hemorrhage syndrome with respiratory failure. Bronchoalveolar lavage and high resolution computed tomography yield additional information on pulmonary activity [10]. Nodules tend to cavitate, and may become the focus of secondary infection with bacterial pneumonia, lung abscess and pleura empyema [5,10].

During evolution of the generalized phase different clinical patterns may be found. After an initial granulomatous phase, evolution of vasculitis occurs and granulomatous inflammation becomes less prominent or wanes [Figure 1]. Evolution of new granulomas, predominantly of the lung, and vasculitis affecting multiple organs are encountered in another pattern of generalization [Figure 2]. Evolution of vasculitis and persistence or progression of granulomatous inflammation may also be encountered [Figure 3]. Different patterns of evolution of generalized WG may indicate differences within the immunological background.

Formes frustes

Limited forms of WG with predominant granulomatous inflammation of the upper respiratory tract and/or lungs in

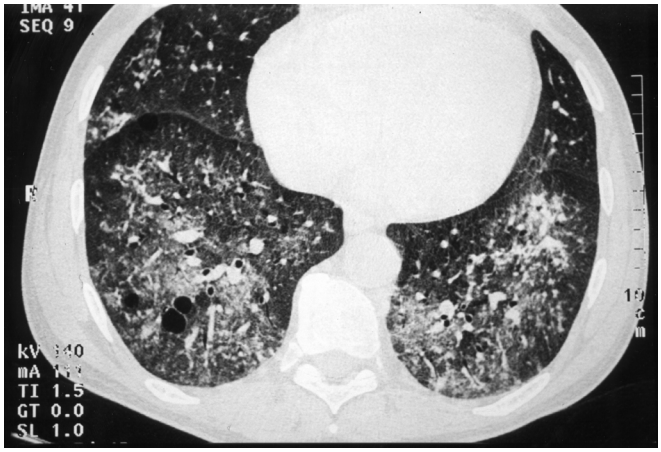

Figure 1. Patterns of generalization: Evolution of vasculitis after an initial granulomatous phase without prominent granulomatous inflammation in the generalized phase. The patient had an initial phase with biopsy-proven granulomatous inflammation limited to the upper respiratory tract (nasal cavity, sinus and mastoid process) lasting for 3 months. Fulminant generalization with pulmonary-renal syndrome, arthralgia, myalgia, palpable purpura, leg ulcers, night sweats, weight loss and detection of c-ANCA and PR3-ANCA were evidenced within 2 weeks. Alveolar hemorrhage and multiple pulmonary infiltrations are seen on this high resolution CT of the thorax.

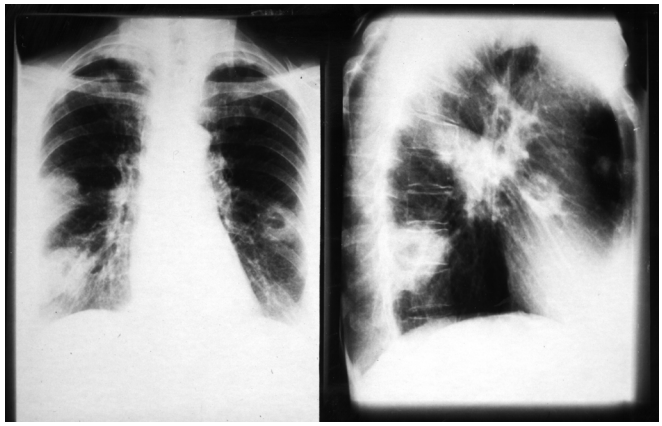

Figure 2. Patterns of generalization: Vasculitis affecting multiple organs, and evolution of new granulomas. After an initial phase with granulomatous inflammation limited to the upper respiratory tract of one year duration, the patient was found to have generalized WG with rheumatic complaints, (biopsy-proven) focal and segmental necrotizing glomerulonephritis, polyneuropathy and c-ANCA/PR3-ANCA. Remission was induced with cyclophosphamide and corticosteroids. Thereafter, the patient experienced two major relapses with night sweats, weight loss, new erythrocyturia without an increase of serum creatinine and a rise in the c-ANCA titer. Both relapses were characterized by an acute flare of multiple, newly developed biopsy-proven granulomas. Multiple nodules with a tendency to cavitate are seen on the patient's thorax X-ray.

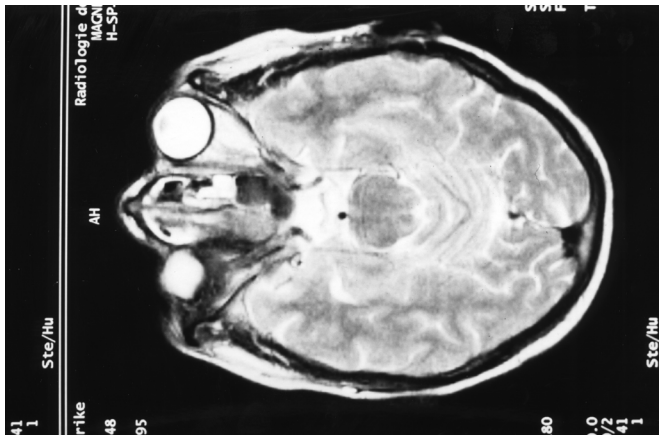

Figure 3. Patterns of generalization: Evolution of vasculitis and persistence of granulomas or slow progression of granulomatous inflammation. Biopsy-proven granulomatous inflammation of the respiratory tract, arthralgia, night sweats, weight loss, episcleritis, purpura and c-ANCA were seen at the initial manifestation more than 10 years ago –retrospe c-tively not permitting a clear-cut delimitation of a biphasic course. Recurrent subglottic stenosis and progressive, destructive, therapy-resistant orbital granuloma, predominantly of the right eye, complicated the course for the next 3 years. Three relapses, confined to the nasal cavity, sinus, inner ear and lung with newly developed nodules, have occurred since. Magnetic resonance images of the head disclosed non-homogenous enhancement of intra-orbital masses encasing the optic nerve and infiltrating the intra-orbital muscles, and intense uptake of thickened maxillary sinus mucosa after contrast administration, suggestive of a granulomatous inflammation, as seen on this image.

the absence of kidney disease, as well as limited forms of granulomatous inflammation and/or vasculitis confined to a few organs, e.g., orbita or gastrointestinal tract, have been reported [11–13]. Some cases in which there is no apparent progression over years [11] seem to represent frozen stages or "formes frustes" of WG. Generalization has been observed in some patients after many years of rather indolent disease [12,13]. As in patients with "classic" WG, an immunological background has to be assumed, which prevents generalization and freezes the disease at the observed stage.

PR3-ANCA-positive vs myeloperoxidase-ANCA-positive WG

Less than 5% of the patients are MPO-ANCA positive, whereas the great majority is PR3-ANCA positive. In PR3-ANCA-positive WG a higher disease extent is seen as compared to MPO-ANCA-positive WG. Renal involvement and extrarenal organ manifestations are found more frequently in PR3-ANCA-positive WG patients than in MPO-ANCA-positive WG. The respiratory tract is involved in a similar percentage of WG patients positive for PR3-ANCA or MPO-ANCA. When MPO-ANCA-positive WG is compared with MPO-ANCA-positive microscopic polyangiitis, respiratory tract involvement is found more often in MPO-ANCA-positive WG and renal involvement more often in MPO-ANCA-positive MPA. There is no difference in the disease extent between MPO-ANCA-positive WG and MPO-ANCA-positive MPA. Thus, apart from their diagnostic value, PR3-ANCA and MPO-ANCA have a role in the pathophysiology of "classic" WG and MPA. Nonetheless, certain clinical features clearly differ between WG and MPA, even when the ANCA specificity is not different [14].

ANCA-negative generalized WG?

A small subset of patients with generalized WG remains ANCA negative throughout the whole course of their disease. This subset seems to have less extended disease with a preference of organ manifestations. Patients present with prominent respiratory tract manifestations, cranial nerve palsies and granulomatous inflammation of the meninges. The preference of certain organ manifestations and the absence of ANCA seem to be a hallmark of these patients and may represent a new subset in WG [15]. Dominance of granulomatous inflammation of the upper respiratory tract and meninges and ANCA negativity point to an immunopathogenesis in this subset of WG patients, which is either different from – or incorporates only certain traits of – mechanisms that are at work in "classic" WG.

PR3 = proteinase 3
MPO = myeloperoxidase
MPA = microscopic polyangiitis

"WG-alike syndrome"

Five patients with a syndrome of chronic necrotizing granulomatous lesions including extensive destruction of the nasal cartilage and bone, small vessel vasculitis, recurrent respiratory tract infections and development of bronchiectasias were recently reported [16]. The Chapel Hill Consensus definition of WG [1] and the ACR criteria for WG [2] could be applied to classify the disease of these patients as WG. Clinical deterioration occurred upon institution of immunosuppressive therapy. Low surface expression of HLA class I molecules was detected. Tissue typing revealed that patients were homozygous for their HLA class I haplotype. The underlying recessive genetic defect was mutations in the transporter associated with antigen presentation genes of either TAP1 or TAP2 transporter molecules, resulting in impaired peptide loading and transclocation of HLA class I molecules to the cell surface. Expanded populations of autoreactive natural killer cells and gd T cells in the peripheral blood, absence of PR3-ANCA and MPO-ANCA, and pronounced infiltration of natural killer cells in the granulomatous lesions were observed [16]. Despite a clinical phenotype resembling WG [1,17], the immunopathogenesis of this disease is clearly different from WG. Thus, we coined this new disease "WG-alike syndrome."

Double granulomatous disease: Two granulomatous diseases in one or one disease with two distinct facets?

The co-existence of ulcerative colitis or Crohn's disease and WG has been reported [18]. Colitis may be the initial presentation of WG in some cases, while in others, chronic inflammatory bowel disease is complicated by extra-intestinal manifestations and/or secondary (immune complex-mediated) vasculitis [18,19]. Pulmonary and gastrointestinal adverse effects of immunosuppressant in the treatment of inflammatory bowel disease and WG are important differential diagnoses. Demonstration of typical Crohn's epitheloid cell granulomas in one location and necrotizing palisading granulomas of WG in another will hardly ever succeed. ANCA testing may yield characteristic findings in support of one or the other diagnosis, i.e., cytoplasmic pattern ANCA (c-ANCA) in the immunofluorescence test and PR3-ANCA in the enzyme-linked immunoabsorbent assay in WG and perinuclear pattern ANCA (p-ANCA) with specificties directed against targets other than MPO, such as non-histone chromosomal proteins of the high motility group 1 and 2 and bactericidal permeability-increasing protein in inflammatory bowel disease [4,5].

Aspects of granuloma formation in WG

"Classic" WG begins with granulomatous inflammation. It is important to stress that the term granulomatous in-

TAP = transporter associated with antigen presentation

flammation does not necessarily mean that granulomas will be found upon biopsy. The granulomatous inflammatory lesions are often less well defined and may take an appearance different from clearly structured "typical" necrotizing palisading granulomas. It is unclear at what stage pauci-immune, necrotizing small vessel vasculitis evolves. It remains to be elucidated whether the initial focus of collagen necrosis in granulomas excludes vascular damage, as Fienberg assumed [17], or whether this focus may be secondary to a capillaritis with capillary leakage of fibrin and subsequent collagen necrosis. "Pure" small vessel vasculitis in the absence of obvious granulomatous lesions in any organ is less common [5].

The granulomatous inflammation evolves from a small focus of collagen necrosis. This focus seems to attract numerous mononuclear histiocytes, followed by lymphocytes, neutrophils and scarce eosinophils. At later stages, the "typical" granulomas of WG develop a well-defined border of palisading histiocytes and interspersed multinucleated histiocytes. Loss of epithelium covering granulomas results in bronchial ulcers. Subsequent evolution of a necrotizing vasculitis affecting small and, less often, medium-sized vessels can affect every organ [17].

Unfortunately, existing animal models do not exactly match human WG. Experimental data on the immunopathogenesis of WG are discussed in the following three sections.

ANCA and vasculitis

c-ANCA are strongly associated with "classic" WG [20–22]. The principal target antigen for c-ANCA in WG is PR3 [22]. Only a few WG patients (<5%) have a p-ANCA with MPO specificity [14]. Combing the detection of c-ANCA in immunofluorescence test and PR3-ANCA in ELISA yields a high sensitivity and specificity for WG [4]. Despite their high sensitivity and specificity, c-ANCA and PR3-ANCA may be found in diseases other than WG, such as sub-acute bacterial endocarditis or severe cryoglobulinemic vasculitis [14,23].

Apart from their diagnostic value in WG, there is substantial experimental evidence that ANCA have a role in the immunopathogenesis of WG ("ANCA-cytokine sequence theory") [4,5]. PR3-ANCA and MPO-ANCA induce *in vitro* activation of cytokine-primed polymorphonuclear granulocytes, resulting in degranulation of PMN and subsequent release of reactive oxygen radicals and lytic enzymes [24]. PR3 is expressed by PMN and monocytes on their cell surface. PR3-ANCA bind to surface-expressed PR3 via F(ab') and Fcg receptor (FcgRIIa) and activate primed PMN [25]. Activated PMN also release inflammatory mediators such as tumor necrosis factor-alpha, interleukin 1 and 8 and leukotriene B4. Production of IL-8 by ANCA-stimulated neutrophils or monocytes within the intravascular department may frustrate transendothelial leukocyte migration. Vascular damage due to degranulation of primed and activated neutrophils may follow IL-8 induced retention of the neutrophils within the intravascular compartment [26]. ANCA induce stationary adhesion of neutrophils rolling on P-selectin expressing platelet monolayers [27]. Endothelial cells are damaged and may become apoptotic by the complex interplay of ANCA, PR3-release of PMN and PMN-endothelial cell interaction [27–29].

The fact that some patients remain ANCA negative has been put forward as an argument against a role of ANCA in WG [30]. However, ANCA-negative WG does not argue against a role of ANCA itself, but is rather an argument in support of our hypothesis that there are different subsets with a different immunopathogenesis that culminate in the clinical phenotype of WG or WG-mimics. Thus, "classic" WG is PR3-ANCA positive, and ANCA are associated with vasculitis in "classic" WG. There are other subsets of a clinical syndrome coined WG, e.g., an ANCA-negative subset [15], and WG-mimics such as the TAP-deficiency syndrome [16]. PR3-ANCA may even have a different "vasculitic potential" in "classic" WG than MPO-ANCA: PR3-ANCA have been found to be more potent in inducing respiratory burst and degranulation of PMN than MPO-ANCA [31].

The role of infection in WG

Chronic nasal carriage of *Staphylococcus aureus* is an important environmental factor contributing to the immunopathogenesis of "classic" WG. A high percentage of WG patients carry *S. aureus*. Relapse rates in *S. aureus* carriers among WG patients are nearly eight times higher than in non-carriers [32]. *S. aureus* carriage and activity of WG in the upper respiratory tract are associated [33]. A prophylaxis with trimethoprim/sulfmethoxazole results in a significant reduction in the relapse rate [34]. Skewing of the TCR Vb repertoire in patients with systemic vasculitis [35,36] may indicate a higher percentage of super antigen-positive *S. aureus* carriers among WG patients with frequent relapses [36]. Staphylococcal acid phosphatase may enter the bloodstream and bind as a "planted antigen" in a charge-dependent manner on endothelial cells. Antibodies to staphylococcal acid phosphatase are found in WG sera. Based on these findings, PMN activation and a subsequent cascade of events leading to pauci-immune vasculitic lesions have been hypothesized [36].

Cytokine profiles in the blood and tissue of WG

As outlined in the above sections, variants of generalization patterns may be found in the biphasic course of "classic" WG. Limited forms or formes frustes, certain subsets of WG (e.g., PR3-ANCA or MPO-ANCA-positive WG, ANCA-negative WG), and double granulomatous disease with features of WG and Crohn's disease are clinically observed. These forms point to differences in the immunological background, giving rise to various clinical phenotypes of "classic" WG and other forms. The

PMN = polymorphonuclear granulocytes

immunopathogenesis in certain subsets of WG patients may be either different from, or will incorporate only certain traits of, mechanisms that are at work in "classic" WG. Recent data on the cytokine profile in WG may point to the relevant mechanisms that will finally determine the clinical phenotype in a patient.

In Wegener's granulomatosis, T cell clones isolated from nasal biopsy specimens displaying granulomatous inflammation and, to a lesser extent, T cell clones and T cell lines generated from bronchoalveolar lavage fluid cells produced a Th1 cytokine pattern. Polyclonal CD4- and CD8-T cells from bronchoalveolar lavage and peripheral blood produced predominantly interferon-gamma. These findings indicate that the Th1 cytokine pattern predominates in T cells derived from the tissue of granulomatous inflammation [37]. Circulating activated CD4-T cells (HLA-DR positive) overproduce IFN-γ and TNF-α during active phases of WG [38]. Moreover, a higher number of IFN-γ positive T cells were detected in nasal tissue of initial-phase WG as compared to generalized WG. In initial-phase WG, a predominance of CD4/CD26 (operational Th1 marker)-positive T cells as well as CD14-positive monoctyes/macrophages has been demonstrated in granulomatous nasal lesions [39]. In patients with generalized active WG, high levels of soluble CD30 ("Th-2 marker") correlate with disease activity [40]. Thus, CD4/CD26-positive T cells and IFN-γ producing T cells may support a polarized Th1-like immune response in granulomatous inflammation of initial-phase WG, whereas in later stages the Th1 response may be less prominent [39].

Granuloma formation is usually a host tissue response to a foreign antigen. In infectious diseases, granuloma formation takes place in the presence of a predominant cytokine profile, e.g., a Th1 cytokine pattern in leprosy or a Th2 cytokine pattern in schistosoma egg-induced inflammatory reactions. In the presence of a Th1 cytokine profile, granulomas are composed of lymphocytes associated with cells of the monomyelocyte lineage, such as neutrophils, macrophages and their derivatives giant cells and epitheloid cells, whereas in the presence of a Th2 cytokine profile granulomas are composed of lymphocytes and eosinophils [5]. Thus, the principal leukocyte composition of a granulomatous lesion is organized in the presence of a predominant cytokine profile. Differences in the cytokine pattern, leukocyte homing capability and organization of the granulomatous lesions and vasculitis, i.e., the immunological background, may cause either "classic" WG or variations and limited forms or formes frustes of WG.

Consequences of the therapy

Until now, stage-adopted immunosuppressive treatment is the mainstay of WG therapy. Myelotoxicity and other severe adverse effects limit the use of these immunosuppressants in individual patients [3–5]. Modulation of the inflammatory response by interfering with the effector mechanisms that contribute to the organization of the granulomatous lesion and vasculitis in WG will imply a more specific way of interrupting the disease process.

Acknowledgments. Many investigators have contributed to our understanding of WG. Unfortunately, not all of them could be cited in this article due to space and reference limitations. The first author (P.L.) is grateful to Drs. Stephan Gadola, Elena Csernok and Antje Moller for many productive discussions on the nature of immunopathogenesis in WG.

IFN-γ = intrferon-gamma
TNF-α = tumor necrosis factor-alpha

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Correspondence: Dr. P. Lamprecht, Dept. of Rheumatology, University of Lobeck, and Rheumaklinik Bad Bramstedt, Oskar-Alexander-Str. 26, 24576 Bad Bramstedt, Germany. Tel: (49-4192) 902-576; Fax: (49-4192) 902-389; email: gross@medinf.mu-luebeck.de.

Capsule

Reshuffling the deck evenly

Reverse transcriptase decodes the genetic information carried by the RNA genome of retroviruses. The viral nucleocapsid protein (NCp7 for HIV-1) is known to function as an RNA chaperone, enhancing the ability of the RNA genome to fold into a stable conformation and promoting annealing of complementary RNAs. Negroni and Buc now suggest that it also promotes genetic reshuffling in the retroviral world.

Because retroviral particles contain two single-stranded molecules of RNA, one mechanism for generating diversity is by homologous recombination in which the reverse transcriptase jumps from one template to the other. Formation of intrastrand stem-loop structures would be expected to influence the location and likelihood of the interstrand base-pairing of homologous regions. When naked RNA was used *in vitro* as a template for reverse transcriptase, two hot spots for recombination were found. However, if the acceptor strand (to which the transcriptase jumps) was allowed to bind NCp7, there was much more recombination, and the greatest increases were observed in areas where recombination had been relatively infrequent. A similar effect was seen with a different chaperone, *Escherichia coli* StpA, indicating that chaperone-mediated RNA folding (and unfolding) may be a general mechanism for more evenly promoting recombination.

Proc Natl Acad Sci USA 2000:97;6385