care community in an ongoing national debate about our health care system, the likes of which had never occurred before.

He continued writing about the health care system right up to the end of his life. Just months before he died, he wrote a compelling article for the New York Review of Books, entitled “On Breaking One’s Neck,” in which he reported his poignant observations on being a patient, having been hospitalized after a serious fall in which he nearly lost his life. Along with very personal commentary on his treatment and eventual recovery, he gave a detailed breakdown of the cost of his care, in a story that characteristically provided critical perspective on the deficiencies of health care in America.

In the increasingly complex world of health care, Bud Relman was a prophetic figure, larger than life. He acted as our conscience. In his writing and speaking, he always reminded us that the medical profession is far more than a business and that as physicians, we have the responsibility to do what is right for patients and for the community as a whole. As distinguished as he was as a researcher, clinician, editor, teacher, and administrator, Bud Relman will be most remembered for the way he fought for a fundamental reshaping of our nation’s health care system. His passionate commitment to that cause will forever secure his position in the pantheon of leaders in medicine.

The Editors

A video interview with Dr. Relman, recorded as part of the journal’s 200th anniversary celebration in 2012, is available at NEJM.org.

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The mTORC Pathway in the Antiphospholipid Syndrome

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The antiphospholipid syndrome is an acquired autoimmune disorder characterized by thrombotic events, miscarriages, and elevated levels of antiphospholipid antibodies. The syndrome is described as secondary if associated with autoimmune diseases, such as lupus erythematosus or rheumatoid arthritis, and as primary if not. The most common thrombotic manifestation of the antiphospholipid syndrome is venous thrombosis, which is usually manifested as deep-vein thrombosis, with or without pulmonary embolism, but arterial thrombosis can also occur, particularly in the context of transient cerebral ischemia or stroke. In rare instances, extensive microvascular thrombosis leads to multiorgan failure involving the brain, lungs, and kidneys, a condition known as catastrophic antiphospholipid syndrome. The mechanisms by which antiphospholipid antibodies cause thrombosis are uncertain (Fig. 1). Current management strategies focus on prevention with aspirin and in some cases with immunomodulatory therapy; once an episode has occurred, treatment includes aspirin, anticoagulants, or both.

Even in the absence of catastrophic disease, the antiphospholipid syndrome can be associated with a vasculopathy that has been best documented in studies of the brain and kidneys. Cognitive deficits, which are more common in patients with the antiphospholipid syndrome than in controls, are associated with lesions in white matter on brain imaging that are suggestive of vasculopathy. The examination of kidney biopsy specimens has shown that renal dysfunction in patients with primary antiphospholipid syndrome is associated with evidence of thrombotic microangiopathy involving small and medium-sized vessels. The limited understanding...
of the pathophysiology of this vasculopathy has hampered the identification of effective therapies and has left experts divided about what constitutes the most effective management. Some experts suggest aspirin for patients with cerebral ischemia, with or without lesions in white matter, and recommend increasing the intensity of anticoagulation therapy in patients with clinical progression. In patients with catastrophic antiphospholipid syndrome, these treatments are often combined with plasmapheresis, glucocorticoids, and the intravenous administration of immunoglobulin, with or without rituximab.

In this issue of the *Journal*, Canaud and colleagues hypothesize that antiphospholipid antibodies, in binding to vascular endothelial cells in the kidneys, brain, or other organs, activate the signaling pathway of the mammalian target of rapamycin (mTOR). In response to extracellular and intracellular signals in the phosphoinositide 3-kinase (PI3K)–AKT pathway, the mTOR pathway regulates cell growth, proliferation, and survival. The mTOR enzyme is a component of two complexes, mTORC1 and mTORC2. The activity of mTORC1 is regulated by a subunit of the regulatory-associated protein of mTORC1 (RAPTOR), whereas the activity of mTORC2 is regulated by a subunit of the rapamycin-insensitive companion of mTOR (RICTOR). However, the two pathways are interconnected. Aspirin and anticoagulants are used for the prevention and treatment of thrombosis in patients with antiphospholipid syndrome. Sirolimus, which inhibits the mTORC1 pathway, has the potential to attenuate vasculopathy.

**Figure 1. Pathogenesis of Thrombosis and Vasculopathy in the Antiphospholipid Syndrome.**

The antiphospholipid syndrome is an acquired autoimmune disorder characterized by persistent elevation in levels of antiphospholipid antibodies, thrombosis, and in some cases vasculopathy. Although multiple mechanisms have been implicated in the pathogenesis of thrombosis, the cause of vasculopathy remains elusive. In this issue of the *Journal*, Canaud and colleagues hypothesize that antiphospholipid antibodies, in binding to vascular endothelial cells in the kidneys, brain, or other organs, activate the signaling pathway of the mammalian target of rapamycin (mTOR). In response to extracellular and intracellular signals in the phosphoinositide 3-kinase (PI3K)–AKT pathway, the mTOR pathway regulates cell growth, proliferation, and survival. The mTOR enzyme is a component of two complexes, mTORC1 and mTORC2. The activity of mTORC1 is regulated by a subunit of the regulatory-associated protein of mTORC1 (RAPTOR), whereas the activity of mTORC2 is regulated by a subunit of the rapamycin-insensitive companion of mTOR (RICTOR). However, the two pathways are interconnected. Aspirin and anticoagulants are used for the prevention and treatment of thrombosis in patients with antiphospholipid syndrome. Sirolimus, which inhibits the mTORC1 pathway, has the potential to attenuate vasculopathy.
antiphospholipid syndrome who underwent renal transplantation. The activation of the mTORC pathways has also been implicated in the pathogenesis of restenosis after percutaneous coronary intervention,\(^9\) a finding that prompted the development of sirolimus-eluting coronary stents.\(^10\)

The limited success of antithrombotic therapy in patients with vasculopathy associated with the antiphospholipid syndrome and the unproven benefit of current immunomodulatory treatments for catastrophic antiphospholipid syndrome highlight the need for improvements. By targeting pathways such as the mTORC pathway, which appears to be causative, sirolimus or other mTORC inhibitors may become the preferred treatment. However, independent confirmation is needed before such an approach is adopted. The clinical outcome data provided by Canaud and colleagues are observational and may be subject to bias, and since antiphospholipid antibodies are heterogeneous, it is possible that only a subset of these antibodies targets the mTORC pathway. Nonetheless, if the authors’ findings are confirmed, patients with mTORC-pathway–directed antiphospholipid antibodies may benefit from sirolimus, not only to improve renal allograft survival but also to prevent the development of vasculopathy — goals that require exploration in clinical trials.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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