already suggests BDNF is not the only biological mechanism mediating the neuroprotective benefits of certain behavioral interventions. What's more, although higher BDNF levels may allow the brain to compensate for awhile, once the pathology progresses to a certain point, it's not enough, Seshadri explained. Multiple pathways are likely involved, as are complex genetic and epigenetic interactions.

"We're in an initial exciting phase," she said. "We need to understand this pathway better; we need to find additional pathways and understand the gene and environment interactions better."

Thus far, a home-run clinical therapy that harnesses brain resilience mechanisms has remained elusive. One drug called davunetide, a peptide derived from a neurotrophic factor implicated in neuronal resilience and protection, showed early promise as a brain-boosting agent in preclinical models of neurodegenerative diseases and improved some measures of memory in patients with mild cognitive impairment (http://bit.ly/1RzoWY5). However, because a recent larger clinical trial involving patients with progressive supranuclear palsy, a neurodegenerative tauopathy, failed to show any benefit from davunetide, further development and testing of the drug have been shelved (Boxer AL et al. *Lancet Neurol*. 2014;13:676-685, http://prn.to/1N5vwX6).

Such challenges underscore the need for a more comprehensive understanding of resilience pathways and gene-environment interactions, which likely will be critical to designing future clinical trials of brain resilience boosting factors, Seshadri said. For example, she noted that a clinical trial of exercise to prevent cognitive decline was negative (Sink KM et al. *JAMA*. 2015;314[8]:781-790). She explained that perhaps only certain subgroups will benefit from particular interventions. Both lifestyle and drug interventions may need to be carefully targeted to subpopulations most likely to benefit.

Large-scale genomic, proteomic, and epigenomic studies have also begun in earnest to help tease out the multitude of factors that contribute to cognitive decline or that protect against decline in the face of pathology, Bennett said. For example, he and his colleagues published new evidence showing that patients with the CD33 risk allele for Alzheimer disease also have higher expression of *TREM2*, another triggering receptor expressed on myeloid cells that functions to counteract *TREM1* (Chan G et al. *Nat Neurosci*. 2015;18:1556-1558). The finding suggests that *TREM1*, *TREM2*, and CD33 pathways may converge to additively suppress the immune response to Alzheimer pathology.

Epigenomic studies in particular might help further elucidate risk factors for cognitive decline. One study found that epigenetic changes are associated with amyloid plaque burden independently of Alzheimer risk genes (Chibnik LB et al. *Ann Clin Trans Neurol*. 2015;2[6]:636-647).

Although these epigenomic changes have not yet been linked to any particular behavioral intervention, Bennet is optimistic that the epigenome might provide additional insights on how behaviors and life experiences may protect the brain from dementia. "A better understanding of [this] biology will help us provide more targeted interventions that are more likely to be effective and adopted," Seshadri added. ■

The JAMA Forum

Can Hospitals Help Create Healthy Neighborhoods?

Stuart M. Butler, PhD

There's a growing recognition that good health depends on "upstream" population health actions (http://bit.ly/1iXkx5p), well before a person enters the health care system, and that community institutions play a key role.

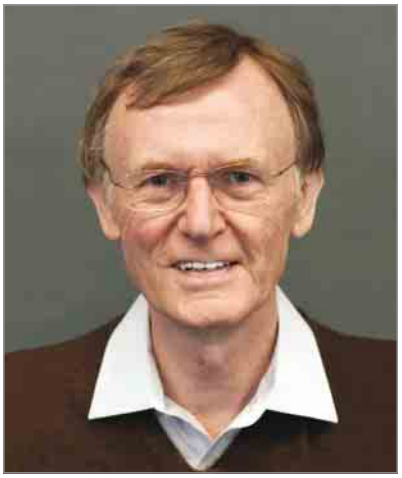
But which institutions are well placed to function as hubs to integrate health care and other services within a community to achieve better health? Certainly, community schools, which are public schools that work with partners to provide a range of health and social services to children, have taken on that role with success (http://bit.ly/1qcjE54).

What about hospitals? Some hospital systems, such as Montefiore Health System in the Bronx, New York, have a long history of collaborating with the local community to tackle upstream problems (http://bit.ly/1HKsHEW). Some others, such as Washington Adventist Hospital in Maryland, are now experimenting with multiple approaches to building healthy neighborhoods (http://brook.gs/1MZpBo6). Indeed, there is growing interest in hospitals playing a greater upstream role (http://bit.ly/1HDA5an).

Motivations for Community Involvement

Traditionally, hospitals have focused more on fixing the results of illnesses and accidents, not on addressing nonmedical factors ultimately affecting health, such as poor housing and nutrition. But the success of "hotspot" strategies (http://bit.ly/1HKt2qV), as well as other initiatives undertaken by the medical system to address the social determinants of health, is prodding many hospitals to rethink their role in the community.

There are now some financial and regulatory nudges, too.



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Since 2012, for instance, hospitals face financial penalties if a higher-than-expected number of their discharged Medicare patients with certain conditions are re-

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admitted to a hospital within 30 days. That gives hospitals a financial incentive to find ways to cut down on readmissions by working with the community and organizing home-based support services (http://nyti.ms/19uiCQr). That's led some hospitals, like Washington Adventist Hospital, to form multiple partnerships with community organizations (http://brook.gs/1MZpBo6). Some intermediaries are helping hospitals in this effort. For example, a nonprofit organization called Health Leads provides college volunteers to hospitals to connect patients with community services (http://1.usa.gov/1SLGhOP).

Another influence is the community health needs assessment (CHNA), enacted as part of the Affordable Care Act (http://bit.ly/1MZsg13). It requires nonprofit hospitals to analyze and report on the health needs of their communities and to develop a strategy to address them. Though still in its infancy, the CHNA likely will encourage more hospital-community partnerships.

"Wrong Pockets" and Other Obstacles

Nevertheless, hospitals face several obstacles when they seek to become more active in improving community health.

One problem is information sharing. Differing data systems make hospital partnerships with local organizations and government agencies difficult. Privacy restrictions on data sharing add to the challenge.

Hospitals also often face the disincentive of a "wrong pockets" problem (http://bit.ly/1RRnvVn). For a hospital, investing in community partnerships is an "out of pocket" cost, usually with no direct financial benefit to the hospital itself (other than, perhaps, an avoided readmission penalty). Worse still for the hospital's bottom line, if the hospital's community outreach means fewer people need hospital services, then the hospital loses business—a classic example of "no good deed goes unpunished." On the other hand, the economic benefits resulting from the hospital's initiatives end up in another pocket—the community and its residents.

The wrong pocket problem is compounded by different government agencies and budgets operating within bureaucratic silos. For example, a good way to reduce health costs and medical emergencies involving elderly people is to focus on such interventions as adapting apartments to reduce the chance of falls and making sure the elderly have good nutrition. Yet when hospitals take the initiative to address these issues, such as Health Leads issuing "nutrition prescriptions" (http://bit.ly/1MZssNC) or hospital nurses making home visits to do safety and kitchen checks, the resultant savings to state or local social service agencies is not identified, measured, and recorded.

Steps Needed for Progress

At least 4 steps are needed if hospitals are to play their full role in improving the health of their communities.

First, there needs to be more attention to developing the metrics required to identify and measure the social and economic benefits of a hospital's community work—the true return on investment.

Second, action is required to make it easier to share information, so that hospitals, schools, and other institutions in the community, as well as government bodies, can coordinate more effectively. One such promising initiative is the Urban Institute–led National Neighborhood Indicators Partnership, which is developing integrated data for community-based partnerships (http://bit.ly/1Mq3Loe). Meanwhile, the Actionable Intelligence for Social Policy program, at the University of Pennsylvania, is helping some counties and cities to integrate data across agencies and cities, so that they can identify the benefits of cooperation and partnerships (http://bit.ly/1MMkMYX). With more data integration and sharing, it will be easier to view the effect of hospital-led initiatives.

Third, to help address the wrong pocket problem, government budgets and payment systems at all levels need to provide flexibility and to blend funds, with the goal of achieving a joint return on investment. If it makes sense for a hospital to incur costs for prevention or nutrition improvement because that leads to reduced social welfare costs, then it's in everyone's interest to provide the right incentive. Thus, part of the savings needs to be shared with the health care budget and the hospital should be appropriately rewarded. Fortunately, some limited progress towards blending housing, health care, and other funds is occurring, thanks to the Medicaid waiver program and pilot programs run by the federal Center for Medicare & Medicaid Innovation (http://1.usa.gov/1NNEhWg).

And fourth, new forms of investment capital are required to finance hospitals to undertake innovative approaches that lead to community benefits but do not result in revenue to the hospital. Some government jurisdictions are beginning to help with this. For instance, the state of Maryland has created a fund to help finance initiatives by hospitals and other institutions that improve community health (http://1.usa.gov/1PqkyNK). Some jurisdictions are also starting to experiment with social impact bonds, which are a type of bond that allows jurisdictions to attract private venture capital that can be used in new ways to fund creative approaches to social goals (http://urbn.is/1Qy5vRj).

Hospitals are usually seen as the last resort in their communities—the place you go when other things fail. Yet they have enormous potential to be partners in improving the general health of the community. Unfortunately, there are obstacles to them playing this role. These need to be fixed. ■

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