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Translational research on aging: clinical epidemiology as a bridge between the sciences

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Using the principles of clinical epidemiology, public health officials were able to organize society to prevent the transmission of disease and premature death well before the basic science mechanisms of such interventions were understood.[1] Using the same principles, the association between aging, disease, disability, and social structures has been recognized for at least a century.[2] Community-based surveys in the 1950s identified a litany of medical, psychological, and social ailments common among older adults. Since that time, dozens of longitudinal cohort studies in multiple countries have reported similar findings: (1) most older adults live independently at home and most of their needs are provided through informal care systems; (2) these older adults suffer from unmet social and medical needs; and (3) the lack of social, economic, recreational, and educational opportunities contribute to disability.[2] These studies also revealed that conditions once thought to be inevitable concomitants of normal aging were, in fact, preventable or could be properly managed so as to prevent excess disability. A cohort study of older adults in 2013 would reach similar conclusions. What continues to change, however, is this boundary between normal aging and disease and, thus, the range of potential targets for medical or social intervention.

In the 21st century, the pathophysiology and cellular mechanisms of certain diseases were found to overlap with the basic mechanisms responsible for cellular homeostasis as well as cellular senescence. Furthermore, scientists reported that changes in the micro and macro environment could modulate these basic cellular mechanisms, and some of these mechanisms may be in a competitive balance. Thus, the mechanisms that protect against cancer might also program cell death, and changes associated with an aging organism might also increase susceptibility to cancer.[3] With a growing understanding of cellular

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mechanisms, are we now poised to influence both the prevalence of age-related disease and slow the rate of aging? Given such tools, could society organize itself in such a way to apply these principles?

This special issue of *Translational Research* provides an update on our progress in translational research on aging. Viewed from a scientist's perspective, our progress over the past century has been astonishing. Viewed from the perspective of public health, our progress has been meandering, poorly integrated, imbalanced, with low impact, and high cost. We can cure some cancers and prevent heart disease, but millions of humans still have no safe drinking water. Our stakeholders are understandably inpatient about the slow rate of translation between basic science discoveries and improvements in the effectiveness and efficiency of public health. While the chorus may have grown louder regarding the importance of translational research, the concept is hardly new. Fifty years ago, President Johnson empanelled a Presidential Commission because cancer, heart disease, and stroke were identified as the new leading causes of death.[4] The President suggested that the excess mortality was due both to insufficient biomedical knowledge and a failure of the benefits of what was already known to reach the public. While tremendous advances have been made in our understanding of basic biological mechanisms, the progression and implementation of these new ideas into practice is too slow—variously described as a gap or a chasm—between what we know and what we do.[5]

To overcome this "translational" gap, much of the current national efforts have focused on developing new research methodologies, new mechanisms of funding research, and the need to create multidisciplinary research teams with expertise in translational sciences. One such 'roadmap' initiative from the US National Institutes of Health (NIH) resulted in the establishment of Clinical and Translational Science Awards in 2006.[6] This new research infrastructure funding mechanism sought to establish "integrated homes" across academic medical centers for supporting clinical and translational research. A key feature of these awards was the mandate to develop research infrastructure through partnerships with academic centers, clinical service providers in the community, and commercial organizations developing novel therapies.[7] Following the funding of about 60 Clinical and Translational Science Awards across the US, the NIH established a new center in 2012, the National Center for Advancing Translational Sciences to manage the network of Clinical and Translational Science Awards as well as promote novel approaches to translating research evidence into effective therapies and clinical interventions.[8] At the request of Congress and the NIH, the Institute of Medicine recently completed an evaluation of the Clinical and Translational Science Awards. The conclusions of this report recognized the need and importance of this infrastructure as well as its future importance in helping move discoveries toward impactful interventions at the level of communities.[9]

As programs such as the Clinical and Translational Science Awards have developed, translational scientists have increasingly recognized the importance of the bidirectional or multidirectional exchange between basic science, clinical medicine, and public health.[10] Before commenting on the articles in this special issue, we turn first to a brief review of the history of aging research as evidence of the fundamental role of clinical epidemiology in facilitating the bidirectional exchange of knowledge between basic science, clinical

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medicine, and public health. We also suggest a continuing role for clinical epidemiology as the bridge between the sciences.

One of the first textbooks devoted to aging was published in 1939 under the editorship of Vincent Cowdry, a cytologist at Washington University in St. Louis.[11] Cowdry's textbook might rate as one of the broadest interdisciplinary treatise on aging ever published. The text included chapters ranging from the aging of plants, to age-related diseases in humans, to mental health in older adults, to the sociology of aging. Writing in the foreword to Cowdry's textbook, Lawrence K. Frank, from the Macy Foundation summarized the state-of-the-art:

> "Two conflicting views are held today by students of aging in man. One considers aging as an involutionary process which operates cumulatively with the passage of time and which is revealed in different organ systems as inevitable modifications of cells, tissues and fluids; the other view interprets the changes found in aged organs as due to infections, toxins, traumas, and nutritional disturbances or inadequacies which have forced cells, tissues and fluids to respond with degenerative changes and impairments. It appears, however, that at least some of these changes serve to maintain functioning and are therefore protective. The issue becomes sharply focused upon the possibility of distinguishing between the cumulative but physiological involutions that inevitably take place in all individuals as they grow older, and pathological changes that occur in aging individuals as the results of adverse environmental conditions."

At the time the quotation above was written, there were no systematic epidemiologic data regarding the scope and magnitude of problems in old age, no antibiotics, and no gene sequencers, among many other post 1940 developments. There was also little understanding of the difference between normal and pathologic aging and, therefore, an ambiguous role for medical care in the problems of old age. An early admonition about the poor care of the aged was published in *Lancet* in 1946.[12] Dr Warren provided a graphic and disturbing first-hand account of institutionalized older adults:

> "Having lost all hope of recovery, with the knowledge that independence has gone, and with a feeling of helplessness and frustration, the patient rapidly loses morale and self-respect and develops an apathetic or peevish, irritable, sullen, morose, and aggressive temperament, which leads to laziness and faulty habits, with or without incontinence. Lack of interest in the surroundings, confinement to bed, and a tendency to incontinence soon produce pressure sores, with the necessity of more nursing, of a kind ill appreciated by the patient. An increase in weight, especially in the anterior abdominal wall, and an inevitable loss of muscle tone make for a completely bedridden state. Soon the well-known disuse atrophy of the lower limbs, with postural deformities, stiffness of joints, and contractures, completes the unhappy picture of human forms who are not only heavy nursing cases and a drag on society but also are no pleasure to themselves and a source of acute distress to their friends. Still, alas, in this miserable state, dull, apathetic, helpless, and hopeless, life lingers on sometimes for years, while those round them whisper arguments in favor of euthanasia."

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Looking back on these 2 quotations and nearly 75 years of aging research, one can identify amazing progress in our understanding of aging and aging-related disease. This understanding has contributed to worldwide improvements in social programs and health care. These improvements have led to an increase in life expectancy in both developed and developing countries. According to the World Health Organization, 80% of people aged 60 and older will live in less developed countries by 2050; this figure is already 65%. Population aging is a worldwide success story and a worldwide health challenge. Unfortunately, the quotations above are both highly relevant and sadly accurate today. As infectious diseases were replaced with heart disease, cancer, and stroke as the leading causes of death, clinical epidemiology began to elucidate risk factors such as cigarette smoking, obesity, physical inactivity, and social isolation. Basic science discoveries not only identified pathologic pathways in these relationships, but also offered potential avenues for treatment of disease. Yet, our ability to actually change behavior, alter environments, and organize society to prevent disease remains limited. Presaging this complexity, Cowdry's 1939 textbook also included an introduction by John Dewey who wrote that:

> "Biological processes are at the roots of the problems and of the methods of solving them, but the biological processes take place in economic, political, and cultural contexts. They are inextricably interwoven with these contexts so that one reacts upon the other in all sorts of intricate ways. We need to know the ways in which social contexts react back to biological processes as well as to know the ways in which the biological processes condition social life."[11]

Clinical epidemiology from the 20th century established the leading causes of death and disability and identified modifiable risk factors. This information has informed US Presidents and other stakeholders to refocus and increase investments in research and public health. This information also moved bidirectionally to suggest studies of biological processes and also to suggest interventions in clinical medicine. Research methods and analytic approaches originally developed for population studies have also been applied to genetic samples to explore associations between genetic variants and disease. More recently, methods of clinical epidemiology have been applied to comparative effectiveness research and to study the outcomes of quality improvement efforts at the level of clinical medicine and public health. Across the multiple bidirectional translation steps from basic science to clinical medicine to public health, clinical epidemiology provides the data that serves interchangeably as a regulatory feedback loop, a catalyst, an alternative pathway, and an overall picture of the health of the nation. However, clinical epidemiology is increasingly tasked to move into a new era that embraces a greater level of complexity.[13]

Rates of disease in human populations, particularly the chronic diseases of the elderly, are likely to be influenced by a complex interplay of genetic and environmental factors.[14] Indeed, environment likely modulates cellular and subcellular processes in both direct and indirect ways. Recent advances in technology involving molecular genetics and the various related studies of the "omics" have now allowed researchers to investigate complex disease models in populations using single blood samples. Notably, when combined with the known socioeconomic risk factors, this greater facility has created new problems. To achieve the statistical power necessary to incorporate these huge numbers of variables in analytic

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models, cohort sizes exponentially larger than the ones currently used in epidemiologic research are required. As researchers also seek to monitor changes in these variables over time, the need for enormous sample sizes or new statistical approaches becomes even greater. It has been suggested that we are entering the age of "mega epidemiology."[13,15]

Various research agencies, including the NIH and in particular the National Heart, Lung, and Blood Institute, have now begun to consider strategies that will allow the best exploitation of these new opportunities with a heightened sense of economy and efficiency. One such strategy is to require much more cooperation and integration of current and future epidemiological studies using common instruments, shared biobanks, and common goals. Another strategy is to emulate the European model of integrating epidemiologic studies with existing national health data bases. This may be more difficult to accomplish in United States at the moment but with the growth of large electronic data systems and regional health information exchanges, as well as the infrastructure of the Clinical and Translational Science Awards, this may be a growing possibility in the near future.[16] These strategies will certainly require the cooperation of large number of researchers from very diverse fields including epidemiologists, clinicians, basic scientists, economists as well as other stakeholders, such as government agencies, the pharmaceutical industry, and advocacy groups, to ensure the wise use of these new opportunities.

In the past, there was little integration within a given epidemiologic study to ensure that a very valuable cohort or sample could be used to address many different hypotheses. These hypotheses might include survey data but could also include biological data with the long-term goal of evaluating potential interventions within the same sample. The collection of biological samples from study participants is a critical link to allow researchers to address disease mechanisms and explore novel approaches for disease therapy. Unfortunately, the history of sample collection within epidemiologic studies has been relatively varied, with many researchers collecting samples with a limited scope for future research and often without the ability to share the sample with other researchers. More recently, there has been a growing awareness that the collection of biological samples from valuable cohorts with often extensive phenotyping is critically important and making these samples broadly available will greatly facilitate the rate of research advances.[17] As a result, highly sophisticated banks of biological samples (ie, biobanks) have been developed that use uniform standard operating procedures to collect, process and store a wide range of biological samples such as whole blood, DNA, RNA, plasma, serum, cerebrospinal fluid, urine, fibroblasts, etc.

Making these samples and the associated phenotypic data available to the research community has resulted in the ability to gather large numbers of samples for genetic studies, particularly genome-wide association studies, which require tens of thousands of samples as well as more recently sequencing studies that are also using ever larger numbers of samples. Centrally storing samples in biobanks is now a key part of the research infrastructure; however, there are still barriers that preclude broader implementation. Chief among these barriers is the cost to store, request, and analyze samples. With the challenging funding climate, ensuring that biobanks remain strong and viable is important—and it is equally important that researchers be able to afford the use of these samples in their research.[18]

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With the use of detailed epidemiologic data and the study of biological samples, researchers have successfully identified epidemiologic and genetic risk factors that are important in not only healthy aging but also aging-related diseases. Prospective studies have now become important to isolate disease mechanisms at earlier stages of development in an effort to identify therapeutic targets and ultimately personalize diagnostic and treatment approaches. Among the areas of aging research with great momentum, studies on Alzheimer's disease (AD) and other dementias have been prominent in integrating epidemiologic, genetic and biomedical and lifestyle factors. AD research is also leading the way toward a new highly collaborative open science approach. A leading example of this is the Alzheimer's Disease Neuroimaging Initiative (ADNI). Begun in 2004, ADNI is a public-private venture that brought together academic clinical investigators from 59 institutions around the United States and Canada as well as many of the leading pharmaceutical, biotechnology, and medical imaging companies working in the dementia field. ADNI launched a large prospective observational cohort study of older adults with amnestic mild cognitive impairment, mild stage AD, and cognitively normal controls. Now in its third phase, ADNI-2, this study has integrated data on clinical and cognitive measures, multiple types of neuroimaging, as well as fluid biomarkers and DNA and RNA for genomic and proteomic studies.[19] A transformative aspect of the ADNI is an open data policy where data sharing with the broad scientific community has resulted in more than 600 manuscripts submitted and well over 300 publications to date.[20,21] Finally, ADNI has spawned the World Wide-ADNI, an international consortium developing parallel cohort studies across all of the major continents. Ultimately the large numbers of affiliated studies with at least partially harmonized protocols will yield a database that can provide sufficient power for following up on promising leads from epidemiologic and clinical studies of AD and related dementias.

It is in this historical context of aging research that the articles in this edition raise such promise for the future. Dr High describes the new workforce and the new infrastructure needed to support translational research. (ref) His article highlights some of innovative junior faculty and physician-scientists training programs that provide opportunities for skill development as well as access to a national community of scholars both locally and nationally. New infrastructure in support of translational research includes animal models and tissue banks, longitudinal cohort studies, standardized assessment tools, and national networks of research centers focused on aging. The National Institute on Aging, (NIA) along with partners such as the John A. Hartford Foundation, Inc, has a longstanding commitment to career development in translational research on aging. In addition, Dr High notes the robust national infrastructure in center programs such as the Alzheimer's Disease Centers and the Edward R. Roybal Centers, among others. Nationally representative cohort studies such as the NIA-funded Health and Retirement Study combine survey and claims data with biomarkers and DNA samples and make these data available to researchers worldwide (http://hrsonline.isr.umich.edu). The NIA has also partnered with the World Health Organization to establish clinical epidemiology studies of aging in representative countries (http://www.who.int/healthinfo/sage). Dr High also expands on the concept of lifespan, which remains relatively fixed at 100 years, with the notion of "healthspan," which seeks to reduce the multimorbidity and functional impairment often associated with aging. A key precept that the fields of geriatrics and gerontology seek to proselytize is the over-riding

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importance of function. Older adults often present with multiple co-morbid conditions, polypharmacy, and changing goals of care. The training programs outlined in this article instruct young scientists to embed these principles in their research design and measurement. Dr High also raises the recurring theme of complexity, which is present at the subcellular, cellular, organism, social, and health system levels. Complexity science has grown to become a new science itself.[22–24]

Using the model of pulmonary disease, the article by Dr Chilosi demonstrates 2 key principles of the complexity in the gene-environment interface. (ref) First, the interplay between genetic predisposition and environmental exposure can not only lead to disease, but may also accelerate cellular aging. Second, some of the pathology and disability attributable to the disease may be due to this “second” pathway of complex processes associated with premature aging. Inherent in these 2 principles is the possibility of impacting individual and population health by avoiding the original exposure, reducing the genetic predisposition, interfering with the disease process, or interfering with the premature aging processes. This article also highlights the role of the loss of immune competence among the failing cellular processes of aging cells. This may represent a target not only for managing chronic lung conditions but may also suggest a target for modulating the aging process in the absence of a specific disease. Franceschi and colleagues popularized the notion of “inflammaging,”[25,26] which is defined as the state when “the beneficial effects of inflammation devoted to the neutralization of dangerous/harmful agents early in life and in adulthood become detrimental late in life.” Dr Chilosi suggests that this delicate balance between the benefits and harms of inflammation may be an important target for individual diseases and aging.

The concept that cellular mechanisms are protective in 1 stage of life or in 1 environmental setting but detrimental in another is echoed in the article by Dr Ershler, which explores why aging and cancer are so closely related. (ref) Dr Erschler writes that “At the cellular level, cancer can be thought of as the physiological alternative to aging.” In other words, a cell, which escapes the processes that regulates replicative senescence, is a cell that will become a cancer. In contrast, a person with an overly active cancer suppressive gene arsenal may be a person destined for premature aging. One interesting conceptualization in the article by Dr Erschler is the classification of tumor suppressor genes as “caretakers” and “gatekeepers.” Caretakers assist in cellular repair and, thus, support longevity of the cell while gatekeepers force cell death in those cells where repair has been ineffective and, thus, prevent cancer. Both Erschler and Chilosi note the finite number of pathways to initiate cell death (eg, telomerase activity) but the clinical heterogeneity that might be expressed despite this 1 final common pathway. For example, cellular senescence may explain the frailty phenotype as well as the loss of specific organ function such as chronic obstructive pulmonary disease.

Dr Kennedy suggests that, if the aging process can be modulated, and if this regulation is by design a feature of human cells that allows for adaptation to a changing environment, then perhaps drugs can be developed to specifically slow the aging process. (ref) The promise of this approach, as outlined by Kennedy, is not so much an increase in longevity as a decrease in those conditions common in older adults such as frailty, cancer, or chronic obstructive pulmonary disease. If, like cancer, processes governing cellular aging are interrelated with the development of other conditions common in aging, then the treatments for “aging” may

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be the preventive medicine for chronic conditions associated with aging. In a model of homeostasis suggested by the aging and cancer story, however, the cost of preventing frailty may be the development of cancer. Dr Kennedy appropriately describes the differences between extending lifespan compared with extending healthspan and compressing morbidity.

The scientific community's current research interest in the connection between chronic human immunodeficiency virus (HIV) infection and premature aging echoes the hypotheses suggested in the articles reported in this issue. The fact that so many people with HIV infection are surviving into old age is an important success story.[27] However, as more of these people reach their fifth and sixth decade with perhaps a 15-year history of antiretroviral therapy, clinicians have noticed a higher than anticipated rate of aging-related diseases.[27,28] These observations, couple with data on the functioning and characteristics of the immune system in HIV-infected individuals, raise the question of whether HIV accelerates the aging process. Furthermore, scientists have posited that this aging process may be modulated through immunosenescence. In a recent summary of the similarities between the biological changes associated with aging and chronic HIV infection, Deeks articulates the potential for a broad new area of translational research: "Many of the biologic factors that are thought to accelerate aging have also been implicated in the pathogenesis of HIV disease. It is the central hope of this review that these two distinct fields of study could merge, as knowledge gained in one could accelerate progress in the other."[28]

Are we indeed on the precipice of slowing the aging process? If we define this slowing as an increase in the longevity at the level of human populations, this process has been ongoing for at least 100 years. Clinical epidemiology has provided the data that shows the changing face and changing risk factors for human disease, age-related disability, and causes of death. Much of this progress has come from interventions that successfully changed a toxic environment but were ignorant to the actual mechanisms of the toxicity. These interventions, which contribute to life expectancy along with preventive health and health care, resulted in a worldwide increase in the number of older adults. The articles in this issue of *Translational Research* provide an important review of how much we have learned about the final common pathways of toxic environments. The articles also provide a glimpse of the delicate balance of cellular mechanisms and the complex challenge of isolating 1 mechanism for change without damaging the entire organism. Finally, this issue demonstrates the incredible potential of large-scale interdisciplinary science that views translation as a bidirectional pathway facilitated by the tools of clinical epidemiology.

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