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Editorial

OBM Geriatrics — An International Open Access Journal for 21st Century Geriatrics Medicine

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Geriatrics, and much of clinical medicine, is on the verge of a profound transformational shift. Until now, there has been a sharp conceptual divide between diseases which can be readily and effectively treated, and diseases which we have thought to be beyond clinical intervention. In the first disease category, are many of the most common infections that respond to antibiotics and immunizations. We have made dramatic changes in the demographics and the mortality of many such treatable diseases. At the other extreme, however, lay the common age-related diseases, for which we could do almost nothing. We have little to offer our patients, except solace, compassion, and bleak acceptance.

We might put this far more accurately and plainly by simply pointing out that *there are no currently available interventions that have ever been shown to affect the underlying pathology of age-related diseases*. None. We generally ascribe this to our inability to affect aging itself. After all, what we do about aging? We shrug our shoulders with an attitude of "we all get old, what can you possibly expect?" Looking at it from an academic perspective, we confess that we can tweak the morbidity and the mortality, we can replace joints or vessels, we can lower risk factors, we can address biomarkers, but we cannot alter the fundamental disease processes that derive from the aging process itself.

Our apparent futility is especially glaring in the case of Alzheimer's disease, but a scrupulous honesty forces us to admit an equal futility if we look at the fundamental pathology of vascular aging, osteoarthritis, osteoporosis, and the host of other age-related diseases that constitute

modern geriatric medicine. We think of these diseases as merely "a part of normal aging" and we surrender any responsibility.

This is not so say that we have no treatments, but it remains true that none of our treatments affect the actual course of the underlying pathology of aging. In osteoarthritis, we can replace the affected joints, but that doesn't address the pathology within the aging chondrocytes, only the patient's ability to use their new artificial joint in daily activity. We don't cure the pathology; we simply replace the problem. In osteoporosis, we can administer drugs, hormones, or minerals, but there is no evidence that we have changed the fundamental decline in the quality or the quantity of the bony matrix or that we have changed the fundamental dysfunction of the aging osteocytes. In vascular age-related disease, we can use statins, stents, or a dozen other approaches, hoping to diminish symptoms and decrease mortality, yet none of these have ever been shown to change the vector of the age-related pathology within the vascular endothelial cells. In short, we have attempted to lower morbidity and mortality – and in some cases with a judicious modicum of success – but we have never yet changed the underlying age-related pathology of age-related diseases at the cellular, genetic, or epigenetic levels.

Contrast this sense of futility with our approach to other diseases that we can't yet cure, but are optimistically confident that we will cure, perhaps soon. For example, we have yet to cure common genetic diseases – such as sickle cell – but we already tout potential gene therapies that may work, and human trials are already in progress for many such genetic diseases. We have yet to cure several metabolic diseases – such as type 1 diabetes – but we see cell replacement techniques that may work and, here again, human trials are in progress for many such diseases. For any number of diseases, we have avenues of approach, we have promising techniques, we have optimism. For such diseases, we nurse a fervent hope, rather than accept a hopeless futility.

Yet for age-related diseases, we surrender to a bleak fatalism. In October of 2015, Margaret Chan (then director general of the WHO) said, in her annual report, that when considering age-related disease, it was time to "give up the curative model". Given an historical perspective, her fatalism, her acceptance of the inevitability of all age-related disease was understandable, but it is exactly that resignation that prevents effective intervention in age-related disease. Most researchers, most clinicians, most academics – indeed most of the public – remain convinced that when it comes to age-related diseases, we cannot realistically hope to alter the underlying pathology: that of aging itself. After all, aging is a fact of life, isn't it?

Historically, a similar fatalism was once the lot of plague, smallpox, puerperal fever, polio, tetanus, and even routine cellulitis. These diseases were "untreatable" so long as the approaches we used were small-molecular, non-biological treatments. However, once we began to think of biological approaches – immunization, antibiotics, antigens, "large-molecular" approaches – we made rapid and unprecedented progress. It was a profound, transformation shift in clinical medicine.

Facts of life became facts of medical care.

This same problem plagues geriatrics: we see no hope of curing many age-related diseases because we cling to a narrow and naïve understanding of the pathology involved, and we restrict our approach to a restricted set of clinical tools – small molecular pharmacology. Once we begin to grasp the deep complexity involved in the aging process and use a more sophisticated set of clinical tools, an entirely new horizon begins to appear. We begin to see age-related diseases as amenable to both prevention and cure, a transformative vision of global clinical – and global

budgetary – problems. These new approaches are based on epigenetic, genetic, and cellular therapies that permit us to reset and restore cell function in ways that are entirely beyond the capabilities of 20th century clinical interventions.

Such approaches are largely grouped under the rubric of regenerative medicine, but the transformation encompasses not only more effective techniques – such as gene therapy – but a broader and deeper understanding of aging itself. We are only now coming to understand the role of cell senescence and changes in gene expression – epigenetics – in age-related disease. We begin to see that age-related diseases are not simply "wear and tear", but a failure to maintain cell function in the face of such wear and tear, a profoundly important distinction. It is not the passive accumulation of damage that causes these diseases, but a gradual failure of active cell maintenance that permits that accumulation of damage. Moreover, such failure to maintain cell function occurs because of epigenetic and not genetic changes. Aging is not a failure of our genes, but a result of a changing pattern of gene expression, a change that can be reset. Our vascular endothelial cells fail not because of serum cholesterol (and dozens of other physiological insults), but because there is a subtle but pervasive change in the pattern of gene expression, and that change results in a failure to deal with those cellular insults.

The key question is a practical one: what is the single, most effective point of intervention?

If we want to cure vascular aging, we should not be naively focused on the individual biomarkers – cholesterol, inflammation, hypertension, *etc*. – but rather we need to focus on the underlying changes in gene expression that modulate the pathology. While we can tweak those biomarkers (using statins, for example) or replace the aging vessels (using bypass grafts, for example), we should be focused on resetting cell function.

As it turns out, this is entirely feasible.

Between the use of cell therapies (stem cells and transformed somatic cells), gene therapies, and telomere therapies, we have an entirely new set of interventional tools, tools that will soon allow us to dramatically change the course of geriatric disease and geriatric medicine in ways that have never been possible. The upcoming revolution will transform our ability to intervene in geriatric disease, finally moving us "from chromosomes to nursing homes".

In *OBM Geriatrics*, we will focus not on ameliorating the diseases of aging, but on curing and preventing these diseases. We will be looking at current and ongoing efforts to not merely lower their mortality and morbidity, but to prevent and cure the diseases that cause such mortality and morbidity. We will foster and examine 21st century medicine, a century devoted to a critical inflection point in the history of geriatric medicine. We will devote our efforts not to accepting that we must live with geriatric diseases, but to showing that we might better live without them.

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