UK research on the biology of aging

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Abstract

Only a few years ago, it could fairly be said that biogerontology research in the UK was in a sorry state. With the exception of the evolutionary biology of aging, which was revolutionised by Britons in the 1950s and in which the UK has remained paramount ever since, the number of research groups whose main focus was biogerontology had waned to single digits, and even those groups were generally very small. This situation has been transformed during the past decade, with the result that the UK arguably leads Europe in this field, in terms of both the quality and the quantity of its output. Moreover, the health of UK biogerontology research seems secure for the foreseeable future. Its one potential Achilles heel is the overemphasis on compression of morbidity as a goal, since further compression is highly unlikely to occur and is anyway inconsistent with the public’s demonstrated desires.

1. Introduction

Is there such a thing as biogerontology? This ostensibly rhetorical question has become hard to answer in the UK in recent years, as work on age-related physiological decline has become interdigitated with fields once viewed—by biogerontologists, but especially by their own workers—as quite distinct. The refrain “I’m not really a gerontologist, but...” is heard almost comically often at British aging meetings. This is a natural occurrence, given that the boundary between aging and age-related diseases is extremely fuzzy (if it exists at all), but in this gerontologist’s experience it has happened more abruptly in the UK than elsewhere. Not only is it a natural occurrence, it is an exceptionally good thing for biogerontology in respect of its standing in biology at large. The vast complexity of the aging process, in some ways outstripping even that of development, has traditionally discouraged young and/or successful biologists from becoming involved in its study, for fear that they (and their careers) will become mired in uninterpretable data. This has, in decades past, given rise to the complementary prejudice that those who do study the biology of aging do so because they could not compete in more tractable subfields of biology. In short, biogerontology has not been respected by biologists in general. This was as true in other countries as in the UK, and is being progressively dispelled there as here; again, however, the abruptness of that process in the UK in the past few years is striking. The bulk of this article is a survey of the many examples that comprise this phenomenon. Several such researchers focus more on specific age-related diseases than on “aging itself”; this again is a step forward, since research into either area can (and frequently does) inform the other.
A major driving force that has brought about this change is the one that might be guessed, money, and especially an improvement in the structure of how it is disbursed. Two initiatives—one governmental, one by a charity—have dominated the transformation of UK biogerontology; they will be described below.

The one area of UK biogerontology that has remained healthy throughout the post-war period is the evolutionary biology of aging. Here, too, however, a transformation has occurred, with specialists in the “why” and the “how” of aging interacting more intensively and productively than ever before. Examples of this will also be noted below.

The number of groups now working on aging or age-related disease in mammals is now so great that an article of this length cannot be comprehensive; accordingly, I have preferentially cited below those groups with whose work I am most familiar, and I apologise to those whose work is omitted. However, I hope to have fulfilled the major purpose of this survey (and of this series on Aging Research Worldwide) by describing the major themes in which research on biogerontology in the UK is particularly strong.

2. Research on the evolutionary biology of aging

The post-war revolution in our understanding of why aging has evolved, or not been evolved away, was due principally to the insights of the British researchers Medawar and Williams (Medawar, 1952; Williams, 1957) and is an area of which the UK has remained consistently at the forefront (Hamilton, 1966; Kirkwood and Holliday, 1979; Charlesworth, 1993; Partridge and Barton, 1993). A particularly welcome development in recent years is that research groups originally dedicated mainly to the theoretical aspects of this topic have become increasingly active on the experimental side, thereby producing work that combines the best of both (e.g. Martin et al., 1998; Sgro and Partridge, 1999). The evolution of aging, like that of any other aspect of life subject to Darwinian selection, occurs ultimately at the molecular and cellular level; hence, evolutionary biogerontologists who are prepared to broaden their expertise to include molecular and cellular gerontology will be better equipped to test their (and others’) ideas. As a result they will progressively eclipse any who remain wedded to an approach based exclusively on mortality data; there is evidently no danger of the UK evolutionary biogerontology community falling into the latter category.

3. Invertebrate model organisms

Compared to many other countries, a relatively small proportion of UK biogerontology is focused on the standard invertebrate models (flies, worms and yeast). Exceptions are the group of Partridge (see above), working with Drosophila, and Gems (e.g. Gems and Riddle, 2000), working with C. elegans. Both groups are based at University College London, and they have recently collaborated to explore the remarkably similar influence of the insulin/IGF signalling pathway on aging in the two organisms (Clancy et al., 2001). S. cerevisiae aging is researched by the groups of Smart (e.g. Powell et al., 2000) in Oxford, Piper (e.g. Harris et al., 2001) in London, and Morgan (e.g. Mankouri and Morgan, 2001) in Liverpool.
4. Research on mechanisms of aging in mammals

Though evolutionary biogerontology has remained pre-eminent in the UK, the number of researchers involved in it has not greatly increased in recent years. This certainly cannot be said of molecular and cellular gerontology.

4.1. Oxidative damage

Several groups, both long- and newly-involved in biogerontology, work on the etiology of oxidative stress and damage in aging. Among the longest-standing are those of Merry (e.g. Lambert and Merry, 2000), focused on caloric restriction in rodents, and Jackson (e.g. McArdle et al., 2001), with specific interests in age-related muscle dysfunction; both groups are based in Liverpool. A valuable complement to Merry’s work is that of the group of Speakman, based in Aberdeen, who study the relationship between metabolic rate and lifespan in mice and other small mammals (e.g. Selman et al., 2001).

The main origin of oxidative damage, including that leading to aging, is generally agreed to be the mitochondrion. It is therefore essential for biogerontology to involve researchers with a detailed understanding of how this most complex of subcellular structures functions—and malfunctions. The Cambridge group of Brand, long prominent in bioenergetics in general and mitochondrial proton leak in particular, has recently broadened its interest in the role of mitochondria in aging (e.g. Brand, 2000).

Additionally, Turnbull’s group in Newcastle studies the deleterious effects of mitochondrial DNA mutations, in aging and age-related disease (e.g. Cottrell et al., 2001) as well as in early-onset mtDNA-linked diseases.

A target of oxidative damage that may be just as important as DNA is proteins; this damage typically results in the production of carbonyl moieties, which are highly reactive and can cause protein-protein cross-linking. One of our most powerful natural defences against this process may be the dipeptide carnosine, which is present at millimolar levels in many tissues. The UK is fortunate to be home to Alan Hipkiss, whose expertise in carnosine biochemistry is second to none and whose work is increasingly revealing how carnosine exerts its effects (e.g. Hipkiss et al., 2001).

4.2. Cellular senescence and nuclear DNA damage

Cellular senescence, the subfield of biogerontology that has perhaps enjoyed (or suffered?) the highest public profile in recent years, is a prime example of the recent resurgence of British aging research, with the sole exception that its growth somewhat predated that of most other disciplines. Before about 1990 only one group, that of Shall, was highly active in the cellular senescence field in the UK (e.g. Karatza et al., 1984); now, by contrast, we can boast highly productive home-grown research groups in numerous locations around the country (e.g. Bridger et al., 2000; Wyllie et al., 2000; James et al., 2000), as well the group of von Zglinicki, previously based in Berlin (e.g. von Zglinicki et al., 2000) but recently transplanted to Newcastle. These are in addition to work on telomere structure and function not directly connected with aging, such as that pursued by Jackson’s group in Cambridge (e.g. Teo and Jackson, 2001).

It is now widely appreciated that other forms of chromosomal damage, particularly double-strand breaks, can trigger cellular responses very similar to those associated with telomere shortening. This has accentuated the interest of biogerontologists in DNA damage over and above its role in cancer, and conversely the interest of DNA damage specialists in aging. The work of Shall’s group must again be noted as having led the way in this regard, with their interest in the role of
poly(ADP-ribo)sylation in DNA strand break repair (e.g. Durkacz et al., 1980). This is the main focus of the group of Burkle (e.g. Beneke et al., 2000), which, like that of von Zglinicki (see above), has recently transferred from Germany to Newcastle. Prominent among groups whose focus on DNA damage and repair has only recently become integrated into biogerontology is that of Cox (e.g. Ongkeko et al., 1999), based in Oxford and now researching the molecular basis of Werner’s syndrome (e.g. Rodriguez-Lopez et al., 2001).

4.3. Aging of specific organ systems

The age-related decline of the immune system has become a particularly strong branch of UK biogerontology in recent years. Groups involved include those of Aspinall (e.g. Aspinall and Andrew, 2000), Akbar (e.g. Plunkett et al., 2001) and Dunn-Walters (e.g. Banerjee et al., 2000) in London, Lord (e.g. Butcher et al., 2000) in Birmingham, Goyns (e.g. Lavery and Goyns, 2001) in Sunderland and Barnett (e.g. Hyland et al., 2001) in Coleraine, Northern Ireland. Aspinall’s group stands out among all UK biogerontology workers—not only those involved in immunosenescence—as maintaining an interest in the actual reversal, rather than the mere retardation, of age-related decline, something that is also a major focus of the present author (de Grey et al., 2001).

The heart is an organ whose aging is distinctive in several important ways: for example, it loses cellularity without losing mass. Boyett’s group in Leeds are prominent in research on the mode of action of the heart’s pacemaker, the sinoatrial node (e.g. Boyett et al., 2000).

Skeletal muscle, on the other hand, loses considerable mass during aging, with multifarious downstream consequences. Aging of muscle is the focus of the groups of Jackson in Liverpool (e.g. McArdle et al., 2001) and Smith in Birmingham (e.g. Smith et al., 2000).

The eye suffers from several major types of aging, of which the most universal is macular degeneration. The group of Boulton in Manchester studies aspects of this process (e.g. Beatty et al., 2001). Glaucoma, another extremely widespread disease of the aging eye, is studied by the group of Webster in Liverpool (e.g. Grierson et al., 2000).

An area often neglected due to its non-life-threatening nature, but no less deserving of basic research for that, is urinary incontinence. This is studied by the group of Ferguson in Cambridge (e.g. Burton et al., 2000).

Groups involved in studying the aging of the nervous system include those of Cowen (e.g. Gavazzi et al., 2001) in London, Edwardson (e.g. Singleton et al., 2001) in Newcastle, Davies (e.g. Fotheringham et al., 2000) in Manchester and Franklin (e.g. Hinks and Franklin, 2000) in Cambridge. Of all aspects of aging, this is perhaps the one where the overlap with diseases often regarded as distinct from “aging itself” is least clear, so highly relevant work on neurodegeneration by UK groups too numerous to list here must also be noted.

Last but not least, the various components of the extracellular matrix are the subject of research by several groups. A prominent example is that of Clark in Norwich, which studies cartilage aging leading to osteoarthritis (e.g. Dean et al., 2000).

5. Funding of biogerontology research in the UK

As noted in the Introduction, the “growth spurt” of UK biogerontology has occurred at least in part because of the improved environment for obtaining funding for such research. Much of the credit
for this must go to the major charity funding biogerontology research, Research into Ageing (RiA). Founded a quarter of a century ago, it has enjoyed a surge of financial success in recent years under the inspirational leadership of Elizabeth Mills, with its income rising nearly threefold between financial years 1994/95 and 1999/00. This money has been used to fund research into all the aspects of aging mentioned in the previous section and more. It has recently merged with the much larger, but hitherto not biology-oriented, charity Help the Aged, a move which is set to provide further sharp increases in its budget for the next two years at least. Mrs. Mills has now stepped down as its head and has been succeeded by Dr. Susanne Sorensen, under whose direction we can be confident that its influence will continue to be considerable.

Partly as a result of RiA’s success, an effort was begun in 1996–7 to address the problem, so familiar to biogerontologists, that our field falls between the two stools of medicine and basic biology. (The UK situation in this regard is exacerbated by our lack of a governmental organisation specifically focused on aging, equivalent to the United States’ National Institute on Aging.) This resulted in the SAGE (Science of Ageing) initiative, whereby the BBSRC (Biotechnology and Biological Sciences Research Council), the government agency with responsibility for funding basic biology research, funded a total of 29 grants totalling £5 million starting in 1998. Many of the groups mentioned in the previous section were funded by this initiative despite never having been funded to work on aging previously, so by that measure it is the main cause of the surge in biogerontology research in the UK.

6. Future prospects

The conspicuous success of the SAGE initiative has led at once to the BBSRC organising a followup, Experimental Research on Ageing (ERA). Applications for this new initiative, which like SAGE will disburse up to £5 million over three years, closed in May 2001; it is rumoured to have been fivefold over-subscribed. Thus, we can look forward with confidence to a continuation of the remarkable volume of high-quality research into aging that is presently undertaken in the UK.

A further measure of the UK’s success in this area is the relatively small number of UK researchers who have recently moved abroad: only two major recent emigrants are known to the present author. This virtual absence of a “brain drain” is a vital requirement for the long-term health of any area of research, so we must hope—and can expect—that it will continue.

The only note of caution that must be raised is with regard to the confusion presently widespread in the UK concerning what research on aging is intended, or likely, to achieve in the medium and long term. Descriptions or “mission statements” published by the funding bodies described above include the following:

The aim of ERA is to understand the basic biology of healthy ageing. It is hoped that such information could eventually lead to new treatments that could reduce age related decline and thus increase “healthspan” and improve quality of life for the elderly. ERA is not aimed at lengthening life span or addressing specific age related diseases such as Alzheimers. (BBSRC, 2001)

Both life expectancy and healthy life expectancy increased between 1981 and 1995; but healthy life expectancy—the number of expected years of life in good or fairly good general health—did not increase by as much as life expectancy. This means that both men and women are living more years in poor health or with a limiting long-standing illness. Research into Ageing is
committed to funding research that will help to close this gap: to achieve a healthspan to fit our lifespans. (Research into Ageing, 2000)

By these words, the UK’s major funders of biogerontology research are committing themselves to contribute to the continuation of the trend termed “compression of morbidity” (Fries, 1980)—the increase of healthspan but not (or, at least, to a lesser degree) lifespan. Noble though this aspiration may be, it is increasingly clear that nothing of the kind will result from our research, simply because medicine that works on robust people (postponing their frailty) tends also to work on frail people (postponing their death). Healthspan is much harder to measure than lifespan, whose “rectangularisation” is now firmly established to have ceased in the Western world about 50 years ago (Wilmoth and Horiuchi, 1999), but the evidence that there is also no ongoing compression of morbidity is likewise now solid (Research into Ageing, 2000; Crimmins, 2001). Thus, the mission statements quoted above are almost certain to be unfulfilled; since it is the public’s money that such bodies are spending, this seems decidedly unsatisfactory (at least to the present author). Moreover, it is wholly unnecessary: the failure of morbidity to be further compressed is due not only to the availability of medicine that prolongs frailty but to its takeup by frail individuals, who thereby demonstrate that they predominantly prefer frailty to death. Thus, biogerontologists should regard undiminished (or even marginally extended) morbidity not as a failure, nor even as the price we have to pay for substantially increased healthspan, but as a bonus. The present tendency to justify funding of biogerontology research on the basis that it will further compress morbidity is not only misleading but illogical. It should be discontinued before its inconsistency comes to the attention of policy-makers and the general public.

References


