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Point of View

A HISTORICAL PERSPECTIVE OF RESEARCH ON THE BIOLOGY OF AGING FROM NATHAN W. SHOCK

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Abstract — This article describes some of the thoughts and the conceptual framework from which Nathan W. Shock prepared his last major presentation. This paper, written some 8 months following Dr. Shock's death on November 12, 1989, is based upon his extensive notes and discussions with one of the authors (George T. Baker). This presentation in no way is meant to encapsulate the long and distinguished career of Nathan Shock, but rather to provide a glimpse of his perspectives on the development of the field of aging. Furthermore, we believe that the scientific principles concerning aging research laid out by Dr. Shock in this publication are still valid today and may provide valuable insights for researchers in the field.

Key Words: aging research, testable hypotheses, mechanisms of aging

A CRITICAL HISTORICAL ANALYSIS OF RESEARCH ON THE BIOLOGY OF AGING

NATHAN W. SHOCK delivered his last major address, "Gerontology, the Study of Aging—Past and Future," at the July 1989 Gordon Research Conference on the Biology of Aging. Four months beforehand, Shock began to review the historical development of biogerontology with the first author; he continued to refine his opinions until his death in November 1989. Shock used as his database references to the papers and works cited in the third edition of Alex Comfort's *The Biology of Senescence* (1979). And although his choice of this particular database was as much for convenience as for its comprehensiveness, it should be mentioned that Shock has at his disposal over 1000 volumes and 27 000 reprints in his personal library, which is now housed in the archives of the Bentley Historical Library at the University of Michigan. It should also be remembered that for nearly half a century Shock meticulously reviewed virtually every publication in the field of gerontology for his *Classified Bibliography of Gerontology and Geriatrics* (1951a, 1957a, 1963) and later for the Shock Index, which was regularly published in the *Journal of Gerontology*.

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Moreover and most critically, each publication was judged more on its particular merit than on the reputation of its author(s). The list by its very nature is highly restrictive but by no means arbitrary. Each citation represented a specific finding, novel approach, or conceptually sound idea applicable to the development of the field of biogerontology. The list of 201 publications Shock selected is reproduced as an appendix to this paper.

Not surprisingly, the list reflects Shock's unwavering commitment to high scientific standards. "Good" science to him meant raising important questions, generating solid data, and evaluating results through tough peer review. At least two other criteria, manifest in Baker's conversations with his friend and a review of Shock's published papers, influenced his selections. On the one hand, Shock singled out publications that serve(d) as building blocks for future work, well-publicized efforts that stood up to the test of time. On the other hand, Shock valued creativity in publications—ones that conveyed novel approaches, challenged the commonplace, and enabled other investigators to break new ground. Shock's list underlines the durabilty of six axioms of aging research he long had advocated:

NATHAN W. SHOCK'S SIX AXIOMS FOR AGING RESEARCH

1. Give me a testable hypothesis. It is worth a thousand theories!
2. Formulate questions to address basic mechanisms of aging and design scientifically rigorous protocols to examine those questions!
3. Focus research on the processes of aging over the entire life span. Studies on older individuals may tell one much about diseases in later life but are not likely to yield information about the basic mechanisms of aging!
4. Aging and disease are not synonymous! There are processes of aging and etiologies of disease. The relationships between the two are important but not inevitable!
5. Aging is a dynamic equilibrium! The rates of aging differ for various systems in any given organism, however, it is the whole organism that ages and dies!
6. Well-documented observations and good scientific data are timeless! Also, don't overlook studies in other scientific fields. Much of our knowledge in gerontology today is a by-product of nonaging research.

I. TESTABLE HYPOTHESES ARE MORE VALUABLE THAN BUILDING THEORIES

Shock was dismayed by the myriad theories of aging that did not specify careful causal relationships, and presentations of evidence that merely documented phenomena without seeking to explain them. "One of the difficulties that we encounter in gerontology, or the study of aging, is that we have a large mass of unstructured and unorganized observational data that has accumulated over the years as a by-product of other investigations" (Shock, 1962, p. 123). Rather than generate "grand" theories of senescence, Shock preferred to formulate testable hypotheses. "The goal of gerontologists is to reduce the dimensions of our ignorance about the basic mechanisms of aging by expanding knowledge about the interrelationships between variables and their relationships to the passage of time" (Baker and Shock, 1991).

The value of testing fundamental principles, argued Shock, was demonstrated in the way scientists showed that homeostasis was a basic mechanism of living organisms. Now viewed as a given, ideas about self-regulating processes advanced by Walter Cannon and

Homer Smith were still not widely accepted in the 1940s when Shock wondered whether they applied specifically to the processes of aging. Shock's own work (1942; Shock *et al.*, 1954) cited in the Appendix (henceforth noted A), as well as that of Adelman (A1970), Engle (A1944), Everitt (A1959), and Witschi (A1966) proved that the mechanism operated on a variety of levels in various species over time. The research publications of Medawar (A1940) and Maynard-Smith (A1958, A1965) had a similar impact: They added prestige to a fledgling enterprise with their questions and hypotheses.

The cumulative work on basic mechanisms in protein synthesis that led to the formulation of the "error" hypotheses of aging offers a more concrete example of how the successful testing of hypotheses can lead to conceptual breakthroughs in a scientific field. Concepts initially put forth by Szilard (A1959) and others on the potential role of mutational events over time eventually gave rise to the more specific "error" hypothesis by Medvedev (1962, A1966) and Orgel (A1963). With the emergence of new immunological techniques, Gershon and Gershon (A1970) were indeed able to demonstrate the presence of altered enzyme proteins with age. Although the observed changes were eventually shown not due to errors in the primary structure of proteins as initially proposed, the testable hypothesis resulted in significant advances in our understanding of how molecular changes occur with advancing age.

Therefore, even testable hypotheses that were eventually disconfirmed proved valuable. This is one reason why Lansing (A1948, A1952, A1964) is prominently featured on Shock's list. Lansing asked good questions and got researchers thinking, even if his initial interpretation of results would eventually be disproven. His concern for measuring the phenomena accurately, moreover, illustrates a second principle Shock held.

II. MEASUREMENTS REPRESENT PHENOMENA—ONLY IF THE RESEARCH DESIGN IS SOUND

Shock was very concerned about the individual and societal consequences of dramatic gains in life expectancy, but he understood that matters of social importance had to be dissected into discrete questions that could be subjected to rigorous analysis. "Research is a technical operation and not all questions can be answered in the form asked," Shock observed. "This formulation of questions and the design of adequately controlled procedures and observations are the essence of research" (1957b, p. 114).

Shock insisted that researchers design experimental protocols that negate age-related or incidental age-dependent variables such as disease or the presence of inhibitors or activators for molecular systems, artifacts due to extraction procedures, and the confounding effects of cohort and period. "The basic biological fact of aging is that the probability of death increases with age in a definite mathematical relationship" (Shock, 1961a, p. 654). Scientists thus should optimize environmental conditions for the entire lifespan of the species under investigation, recognizing that "optimal" conditions may differ at successive stages. To Shock, there was no "good" or "bad" animal model system per se. Bad experiments, however, suffered from flawed experimental paradigms and inappropriate techniques.

In this context, Shock praised Loeb's work (A1908) on the *Drosophila,* one of the first to measure rates of aging. Berg's analysis of nutrition's effects on longevity (A1960) is another classic, important for the way it quantified pathological influences. Shock admired works that tied together phenomenological information methodologically.

Sacher (A1956, A1958, A1959, A1968, A1975, A1976), for instance, was a good field biologist; his mathematics were not necessarily all that sophisticated, but they were robust enough to generate important anthropometric studies of longevity. Baker (A1976), Banga (A1957), Falzone *et al.* (A1959), and Goldstein (A1969) showed sensitivity to the nuances of how an experimental design might distort results.

Possibly the most vivid instance where attention to method and design advanced gerontologic thinking is evident in the work with in vitro cells. Based on experiments with chicken hearts, Carrel (A1912) had claimed that cells could live normally forever outside of the body. Hayflick and Moorhead (A1961) initiated a series of studies (Hart and Setlow, A1974; Hayflick A1975; Holliday and Pugh, A1975) that disproved Carrel's hypothesis. Basic correlations of senescence found in vivo held in vitro. Demonstrating the importance of studying developments over time prompts a third axiom.

III. STUDY MECHANISMS OF AGING, NOT JUST THE AGED

Some gerontologists investigate only "old" subjects. Others choose not to differentiate between the processes of development and aging (Schroots, 1988; Yates, 1991). Early on, Shock opted for a centrist position: "In the broadest sense, problems of growth, development, and maturation are as much a part of gerontology as are those of atrophy, degeneration, and decline. However [attention] will be confined to changes that occur in later maturity and senescence" (1951b, p. 353).

Shock's work on the Berkeley child-development studies and in shaping the Baltimore Longitudinal Study of Aging convinced him that gerontologic research required comparisons at least at two points after maturity. Only this way could age *changes* be distinguished from age *differences* within a population. If results were to have general applicability to basic mechanisms of aging processes, moreover, Shock felt that research should be conducted on wild-type strains of various species. Highly inbred strains may be convenient for researchers because they exhibit less variance in any number of biochemical and physiological traits as well as survivorship, but they may not reflect normative processes of aging.

Many of the choices Shock made reflect his interest in mapping developmental changes and constructing life tables. The inclusion of Tanner (A1955) underlines Shock's interest in life transitions that have long-term effects. He esteemed the work of Pearl (A1927, A1940), who did experiments to test hypotheses concerning rates of change in senescence. Similarly, Dublin *et al.* (A1949) did more than measure life expectancy; these studies of mortality rates had a theoretical basis, which gave structure to future work.

The cluster of papers concerning basic mechanisms in various parts of the organism aptly tie together Shock's first three axioms. The pathways into neurobiology illuminated by Finch (A1972, A1976); Walford's descriptive studies of autoimmunity (A1962); and the work of Makinodan (Makinodan and Peterson, A1966; Mackinodan *et al.*, 1971a,b), Price (A1971), Burnet (A1961, A1970), and their colleagues on immunology all attest to the need for collaborative teams of specialists who have the complementary skills needed to do gerontologic research. The work on free radicals generated by Harman's laboratories (A1955, A1961, A1965, A1968, A1971) and others (Kohn and Rollerson, A1960; Kohn, A1971) fits this pattern: A unified concept explained mechanistically the morphological, biological, and physiological processes of aging in a series of testable hypotheses. Their work strengthened the next rule.

IV. AGING IS NOT A DISEASE

"Perhaps one of the most useful contributions of gerontologic research has been the demonstration that aging is not necessarily associated with deterioration and disease" (Shock, 1961b, p. 16). Shock considered this simple observation the sine qua non of his research career. Chronic disease and aging were synonymous in many minds, he felt, not just because of stereotypes deeply rooted in the culture (Achenbaum and Kusnerz, 1978), but because those who professionally deal(t) with late-life problems saw mainly elderly people who suffered some debility. To demonstrate that aging was not a disease sui generis, Shock pointed to basic research that bolstered his position.

Lorand's pioneering work (A1904) and Sheldon's (A1949) merit attention in this regard. Not only did they question the inevitability of senility, but they asked key questions that soon would dominate the field. Three decades ago, when Libow summarized existing evidence concerning differences between normative aging and disease processes (A1963), most professionals still hewed to outmoded concepts. Hence Gitman's (A1969) clinical guide that put disease of late life into diagnostic contexts *and* discussed "normal" phenomena of aging signaled an important shift in thought. And Shock praised early synthetic works—Birren (A1961) and Blumenthal (A1945)—for their emphasis on disentangling the effects of age and disease. This theme received a somewhat different statement in the next axiom.

V. UNDERSTANDING BASIC MECHANISMS REQUIRES ATTENTION TO WHOLE ORGANISMS AND INTERSPECIES COMPARISONS

Elaborating the theme of multidimensionality evident in Cowdry's landmark *Problems of Aging* (1939), Shock contended that "the problems of gerontology extend from questions of changes in enzyme conditions within individual cells to important social and economic problems of the interrelationships between aged people themselves and other members of society" (1951c, p. 1). Scientists had to understand the physiological consequences with advancing age of a change and/or an alteration of the system they studied in relation to the whole animal. "Because of the diversity of rates of aging among different individuals as well as between different organ systems within the same individual, it is obvious that no specific answer can be given to the question, 'When does old age begin?'" Shock observed. "Aging is a dynamic equilibrium. The individual animal at any age is a result of processes of accumulation and degradation that take place simultaneously" (1951d, pp. 1–2).

This is why Shock, a developmental physiologist, kept abreast of research in evolutionary biology. He evaluated results in terms of what an organism was evolutionarily designed to do. And he considered interspecies comparisons appropriate because aging was a universal, biological phenomenon. Significantly, his plans for an "ideal" research institute of gerontology in the 1950s included facilities for rearing and maintaining unicellular mechanisms, insects, dogs, cats, and so on (Shock, 1957b, p. 173).

Shock's emphasis on comparative analyses probably explains why many of the articles he considered notable concern organisms with which he had little firsthand experience. Such diverse projects as Flower's early studies of molluscs (A1922) and tortoises (A1945), the Szabo work with snails (A1929), and Thung's anthropometric analyses (A1962) all dealt with issues of growth and longevity. The more comparative baselines available to chart basic mechanisms and rates of aging, the more likely scholars would comprehend

"natural" aging. Similarly, Shock's interest in research on inheritance—Jalavisto (A1950), Kallman and Sander (A1948), and Rockstein (A1958)—was yet another pathway for examining intraspecies differentials in rates of change at the genetic and organic levels. That this pioneering work has been refined by subsequent scholars did not diminish its value to Shock.

VI. SOLID DATA DO NOT LOSE VALUE BECAUSE THEY ARE OLD; A GENUINE SCIENTIFIC SPIRIT NEVER FADES

It is revealing that only 19% of the 201 articles on Shock's list of major publications that facilitated biogerontology's development were published before 1939. This was the year that Cowdry's *Problems of Aging* appeared; Shock called the volume the first "modern" work of this emerging scientific field. Almost 60% of the works were published before 1959, when the first of the three handbooks of aging prepared by the Inter-University Training Project in Social Gerontology were issued. One might quibble about the historical representativeness of Shock's list—he was, after all, using a data base already 10 years old at a time when some claimed that "knowledge in biomedicine has a doubling rate of approximately three years" (Schneider and Rowe, 1990, p. xvii). But more than most, Shock knew that the truly important questions in gerontology were perennial favorites. A review of the abstracts of the 1940s, moreover, indicated why breadth of vision was indispensable:

> A good share of our knowledge about aging has come from studies where age data were a by-product of other research programs. Furthermore, many articles appear as a single contribution from many different laboratories throughout the country. Relatively few originate from laboratories where aging is a major concern. (Shock, 1951c, p. 75)

Regardless of where it is done, attention to fundamental issues, exemplary research designs, and peer review are essential for gerontologic progress.

No wonder, then, that the list compiled by one of gerontology's truly cosmopolitan scientists should include publications by so many international scholars. The very eclecticism of references has didactic value. The mention of Crocker's work on aging in plants (A1939) serves to remind us that early ideas about "senescence" came from botany; the multiple references to Lack's work with birds (A1943, A1954) attest to a scholar's voracious appetite to learn as much about aging as possible. Yet Nathan Shock was no amateur: Even one extended conversation with Shock communicated his disdain for much that passed as "research" in some areas of gerontologic expertise. Nor was Shock the type to express his hopes for gerontology in teleological terms. As this list indicates, Shock put his faith in good research because common sense and years of experience persuaded him that solid, basic work would yield the most useful gerontologic science.

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APPENDIX: THE SHOCK LIST

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