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COMMENTARY | Genetics inMedicine

Archibald E. Garrod: the father of precision medicine

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In his 2015 State of the Union address, President Obama launched the Precision Medicine Initiative (PMI). In brief, the goal of this ambitious initiative is to improve health by tailoring the prevention and treatment of disease to genetic, environmental, and lifestyle differences among individuals. Because of progress in sequencing the genomes of cancer cells and in identifying mutations that are "drivers" of malignancy, the PMI will initially be focused on cancer therapy, but it is hoped that it will ultimately offer new avenues for the amelioration of many diseases.[1] Here, at the outset of the PMI, it seems to be an appropriate time to recall the contributions of Archibald Garrod (1857–1936), who was the first person to appreciate the ubiquity of individual variation (or "chemical individuality") in both health and disease and is the intellectual father of precision medicine.

Archibald Garrod is best known for his book *Inborn Errors of Metabolism* (1909), in which he argued that four diseases—alkaptonuria, albinism, cystinuria, and pentosuria—were inherited as Mendelian autosomal recessive traits.[2] This prescient work opened the study of genetic diseases and established Garrod's reputation as the founder of medical (biochemical and molecular) genetics.[2] But Garrod's accomplishments extended far beyond the study of inborn errors of metabolism. Here, we stress his remarkable insights regarding the significance of individual variation. In 1902, Garrod published "The Incidence of Alkaptonuria: A Study in Chemical Individuality,"[3] a paper that served as the basis for *Inborn Errors of Metabolism* and a second book, *The Inborn Factors in Disease* (1931).[4] In this paper, Garrod suggested that "alkaptonuria is not the manifestation of a disease but is rather of the nature of an alternative course of metabolism." This view may be open to question because the accumulation of homogentisic acid and its metabolites in the tissues of individuals with alkaptonuria often results in early-onset osteoarthritis and may also cause other health problems, but it led Garrod to a most important insight: "the thought naturally presents itself that these [alkaptonuria, albinism, and cystinuria] are merely extreme examples of variations of chemical behaviour which are probably everywhere present in minor degrees and that just as no two individuals of a species are absolutely identical in bodily structure neither are their chemical processes carried out on exactly the same lines."

Garrod advanced the idea of chemical individuality further in *The Inborn Factors in Disease*. (In the early 1900s, "factor" was a commonly used term for gene.) He discussed chemical individuality in the context of Darwin's theory of evolution by natural selection and by considering disease as an "agent of evolution" (p. 53). After calling attention to some of the chemical differences among species, he wrote "there is room for immense variety and for differences not only between species and genera, but also between individuals of a species" (p. 41). Chemical individuality provides the basis for what historically had been called "diathesis"—an individual's "disposition, or predisposition, to a particular malady or group of maladies" (p. 10). For instance, the natural history of gout illustrates that "the diathesis is regarded as latent, but its presence is revealed by the manifestations to which it gives rise from time to time" (p. 12). Although Garrod was personally interested in the "inborn factors" that predisposed people to particular maladies, he recognized the importance of environmental conditions in the manifestation of inborn errors of metabolism. In terms of genetic epidemiology and public health, we might think about the genetic and environmental factors that contribute to a disease phenotype as "risk factors." Using a lovely metaphor, Garrod wrote, "Individual cases of any particular disease… are not exactly alike…; they resemble rather the drawings made from the same model by individual members of a drawing class" (p. 31). Garrod further emphasized the need for understanding individual variation of disease in evolutionary terms and for interpreting these diseases using evolutionary insights: "As to what constitutes fitness to survive, man and Nature do not see eye-to-eye… The whole aim of medical art, whether therapeutic or preventive, has been to counteract the laws of Nature" (p. 53).

Archibald Garrod exemplified what, in today's words, we would call a physician–scientist. He was actively involved in laboratory studies of his patients. He understood that many individual variations produced no outward effects and could be recognized only by chemical analysis. Nonetheless, he repeatedly stressed the value of clinical medicine. Thus, he wrote, "It is in the ward rather than in the laboratory that the importance of inborn factors is to be appreciated" (p. 23). As a physician he emphasized the need for a detailed and comprehensive understanding of individual patients, because "The constitution of a man is the sum of *all* his qualities, his bodily form, the structure of his tissues, his coloration, height, weight, blood pressure, and body temperature; … and tricks of gesture and action. In all or some of these respects, each man differs from all his fellows, for even uniovular twins are not exactly

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alike" (p. 147). Perhaps more tellingly, he wrote that the physician "realizes that each [patient] is an individual, and not merely a member of the human race. The task of the practitioner is far more than to apply the knowledge supplied to him from the laboratories; he … calls upon his experience to guide him as to how he may best help the particular patient [manage his disease] with the least possible damage" (p. 24). These passages could be taken as the first clear statements of the goals of precision medicine.

Garrod was one of the most highly acclaimed physicians of his day. He was elected a Fellow of the Royal Society and was knighted. In 1920, he succeeded William Osler as Regius Professor of Medicine at Oxford University. Given his prominent position in the medical community, it is perhaps surprising that his ideas on chemical individuality were not more rapidly and more widely accepted. There may have been several reasons why his work was long ignored, including that medicine was still in thrall of the germ theory of disease and therefore physicians were focused on external rather than inborn factors in disease. Indeed, before Garrod demonstrated that alkaptonuria was a heritable disease, a prominent theory was that it resulted from a gastrointestinal infection.

Since Garrod's time, numerous studies of biochemical individuality,[5] electrophoretic demonstrations of protein polymorphisms,[6] and, more recently, genomic analyses have amply documented the ubiquity of individual variations even among healthy persons, with their clinical relevance firmly established, thus setting the stage for the PMI.

In *Genetic Medicine*, Barton Childs[7] compared the perspectives and the influence of Osler and Garrod in the practice of modern medicine. In Childs's words, "No one would deny that Osler was the hero of the medicine of the twentieth century. It is likely that Garrod will be the icon of the twenty-first" (p. 16). If precision medicine lives up to the expectations of its proponents, then Childs's prediction may well come to pass.

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DISCLOSURE

The authors declare no conflict of interest.

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