Perspectives

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ARCHIBALD EDWARD GARROD, the Reluctant Geneticist

Alexander G. Bearn

The Rockefeller University, New York, New York 10021-6399

THE name ARCHIBALD EDWARD GARROD (1857–1936) is familiar to most geneticists, particularly those interested in the historical roots of biochemical and human genetics. The seminal work by which GARROD is identified, *Inborn Errors of Metabolism*, was delivered as the Croonian Lectures in June, 1908 to the Royal College of Physicians in London and was published the following year [GARROD (1909), reprinted in HARRIS (1963)].

The substance of these lectures is now a genetic commonplace: errors in metabolism are often inherited in a recessive fashion and are due to the absence of a critical enzyme in a metabolic pathway. The lectures failed to arouse any enthusiasm from his audience and were received only perfunctorily by the medical press.

The extension of these ideas to the important concept of biochemical individuality may have originated when GARROD read CARL HUPPERT's (1834–1904) impressive rectorial address at the Carl Ferdinand University in Prague in 1895, entitled "On the Maintenance of the Characteristics of Species" (HUPPERT 1896). HUPPERT, a physiological chemist who had been trained by CARL LEHMANN (1812–1863), advanced the view that chemical differences between species must exist and that these differences express themselves as unique chemical structures. In the course of his lectures, HUPPERT suggested that interspecies differences in susceptibility to infective agents resided in the species' possessing different chemical structures that were probably protein in nature. Resistance to infection in certain species could be laid at the door of unique chemical structures that were inhospitable to the invading infectious agent. HUPPERT's evolutionary interest led him to assert with foresight, "The nucleins and nucleoalbumins which derive from the cell nucleus . . . play the primordial role in life itself . . . an uninterrupted chain of specific chemical characteristics linking antecedents and descendants."

When HUPPERT made these far-sighted remarks, ARCHIBALD GARROD, whose father was a Harley Street physician who discovered that uric acid played a prominent role in the causation of gout, had launched his consulting practice in London and was intent on honing his medical skills. In addition to pursuing the purely clinical work necessary to support a growing family, GARROD was energetically applying spectroscopic methods, which he had originally learned while an undergraduate at Oxford, as an aid to medical diagnosis. His immediate goal was to explore the nature of the chemical substances that conferred the distinctive coloration to the urine in normal individuals as well as in patients with a variety of diseases. Working collaboratively with GOWLAND HOPKINS, a future Nobel Laureate in medicine or physiology, GARROD noticed that patients who had been treated with sulfonal, a sedative drug, excreted a reddish-colored urine whose color he and HOPKINS went on to identify as hematoporphyrin. In 1900, while GARROD was continuing his spectroscopic studies on colored urine, the celebrated trio of DE VRIES, CORRENS and TSCHERMAK rediscovered the works of GREGOR MENDEL and, almost immediately, the naturalist WILLIAM BATESON became GARROD's most articulate and spirited disciple.

A year earlier, pursuing his interest in colored urine, GARROD had presented a paper to the Royal Medical and Chirurgical Society in London that would mark the beginning of a life-long career devoted to the study of human metabolic disease and led, a decade later, to his Croonian Lectures. GARROD's paper was on alkaptonuria, a rare condition then colloquially known as "black urine disease." Those with the disease were usually free of symptoms, but they "advertised their condition," to use GARROD's phrase, by passing urine that turned black on standing because of the presence of homogentisic acid. Without explanatory comment, GARROD (1900) recorded that the condition was usually congenital and frequently occurred in brothers and sisters. While continuing his clinical practice, GARROD became increasingly fascinated by the disease. On November 30, 1901, GARROD, in an article in *The Lancet* entitled "About Alkaptonuria," made the trenchant observation, "I am able to bring forward evidence which seems to point, in no uncertain manner, to a very special liability of alkaptonuria to occur in the children of first cousins"

(GARROD 1901). This association, he wrote, "can hardly be ascribed to chance and further evidence bearing upon this point would be of great general interest." Further evidence was soon to come. The following month, BATESON referred directly to GARROD's work on alkaptonuria. In a footnote to his Report to the Evolution Committee of the Royal Society, he pointed out that one-quarter of the cases of alkaptonuria reported by GARROD were the offspring of cousin marriages (BATESON and SAUNDERS 1901). This fact could be simply and easily accounted for if the condition was inherited in a recessive fashion, according to the recently discovered laws of MENDEL.

GARROD immediately recognized the evident truth of BATESON's suggestion. The familial aggregation of patients with alkaptonuria, the rare transmission of the trait from parent to offspring, and the consanguinity could all be explained on the basis of recessive inheritance. He understood clearly the implications of recessive inheritance, and in a playful moment he wrote slyly to BATESON, "I do not see any way of introducing any marriageable alkaptonurics to each other with a view to matrimony."

Extending the concept of Mendelian inheritance, GARROD proposed that inherited variations could lead either to a relatively simple "metabolic sport" such as alkaptonuria or, more complicatedly, to structural abnormalities including congenital malformations, such as Down's syndrome. As he adroitly put it, "Bodily form and chemical structure go hand in hand." GARROD, particularly in his later years, is so often portrayed as a genial, white-haired, unassuming, patriarchal physician of extreme modesty, that it is wonderfully refreshing to read in one of his early letters to BATESON, "I would ask that you kindly not speak of [my ideas] to others, insofar as they may contain anything new."

With enthusiasm and dogged determination, and by writing to physicians throughout the world, GARROD collected, in addition to patients with alkaptonuria, families with albinism, cystinuria and pentosuria, conditions he also regarded as recessively inherited. It was these four metabolic diseases that formed the core of his Croonian lectures. In addition to summarizing his extensive experience with these diseases, GARROD made a bold and novel intellectual leap. These thoughts were summarized in a landmark paper in *The Lancet*, published in 1902. He proposed that the concept of inherited deficiencies of an enzyme as a cause of recessively inherited diseases could be made biologically generalizable. Individual biochemical variation was not only the biological norm, but also the sovereign hallmark of human nature.

Only occasionally would the hereditary biochemical individuality be so extreme that it would result in overt disease. With these thoughts GARROD's medical fascination with inborn errors of metabolism continued but, as the years passed, he became increasingly absorbed by the broad spectrum of individuality, its chemical and biological as well as its medical significance, and what it might mean from an evolutionary point of view.

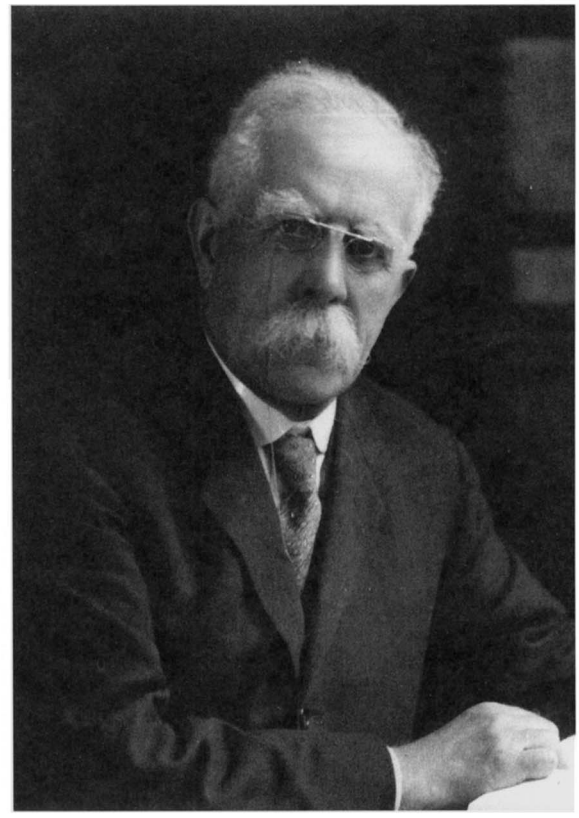

FIGURE 1.—ARCHIBALD EDWARD GARROD

Although GARROD was a pillar of the medical establishment who had received the highest honors and had become Regius Professor of Medicine at Oxford, the profession never appreciated the broad biological significance of his work. A well respected, competent physician, he never enjoyed the routine, often monotonous, aspects of the profession. He frequently wondered why he had chosen to pursue a career in clinical medicine and consultant practice. He was, as he freely admitted, "a wanderer down the by-paths of medicine," and that is exactly the way his contemporaries regarded him.

GARROD gradually became more and more convinced that biochemical variation was an essential clue to an understanding of evolution and that even human disease must be considered and taught in an evolutionary perspective. In the final analysis, it was biological individuality that determined susceptibility or resistance to human disease.

After GARROD retired in 1927 as Regius Professor of Medicine, released from the daily responsibilities of a busy professional life, he had more time to assemble the ideas that had been steadily forming during his 40 years as a practicing physician. He now wrote what was his crowning intellectual achievement.

GARROD (1931) could not bring himself to dignify *The Inborn Factors in Disease* as a book, preferring instead to call it "an essay." There is no evidence that this elegant and perceptive essay was appreciated any more than *Inborn Errors of Metabolism.* When GARROD first proposed to the Oxford University Press that they publish *The Inborn Factors in Disease,* they "assented palely" and agreed to do so only because GARROD was a Delegate to the Press and they had already published *Inborn Errors of Metabolism.* The Secretary continued, "He will not pay for it. I don't see how we can very well avoid doing this. It ought not to cost more than £100, and might even sell a few copies." In the event, they printed 1250 copies. Even GOWLAND HOPKINS, to whom he had dedicated the second edition of *Inborn Errors of Metabolism* (1923) and who a year later linked GARROD's name with JUSTUS LIEBIG as one of two Fathers of Biochemistry, did not refer to *Inborn Factors in Disease* in his otherwise sensitive and appreciative obituary of GARROD for the Royal Society. The recent facsimile publication of this "essay," edited and thoughtfully annotated by CHARLES SCRIVER and BARTON CHILDS (1989), should do much to rekindle interest in this wise and insightful book.

After GARROD's death in 1936, physicians continued to remember him as the author of *Inborn Errors,* but it was the biochemists who were the first to recognize the biological importance of GARROD's work. Alkaptonuria made its way into MEYER BODANSKY's *Introduction to Physiological Chemistry* in 1927, although he did not refer specifically to GARROD. ROGER J. WILLIAMS, also a biochemist, devoted a paragraph to alkaptonuria in his *Introduction to Biochemistry* in 1931, but did not develop the concept of biochemical individuality until he wrote his influential text, *Biochemical Individuality,* in 1956, 20 years after GARROD's death.

Despite GARROD's profound impact on the field of genetics, he remained a busy practitioner of medicine who preferred to stand on the sidelines while BATESON battled furiously with the biometricians. When the Genetical Society was founded in 1919, GARROD did not become a member, nor did he attend meetings of the Society, even as a guest. Although he, with his friend GOWLAND HOPKINS, was one of the Founding Committee Members of the Biochemical Club that met in March, 1911, he soon resigned from the Committee and, surprisingly, does not seem to have played an active role in the Society thereafter. Less surprisingly, GARROD had similarly shown no interest in joining the Eugenics Education Society inspired by GALTON and founded in 1907. That Society was largely devoted to popularizing the eugenic doctrine, and GARROD wanted no part in it. When the horticultural geneticist, CHARLES C. HURST, created a Council to further research in human genetics in 1931, he urged GARROD to become a founding member. GARROD was supportive and encouraging, but he was now 74 years old, and his age and deteriorating health deterred him from getting actively involved.

GARROD, ever careful to avoid giving the impression that he understood the mathematical consequences of Mendelian inheritance, wrote in a letter to LIONEL PENROSE in 1934, "Hogben in his paper on alkaptonuria in the *Edin.* (sic) *Royal Society Proceedings* and in his 'Nature and Nurture' has, I think, given me more credit than I am entitled to, seeing that it was Bateson who saw daylight." A year earlier, in a letter to E. A. COCKAYNE, a friend and dermatologist, he wrote, "I find myself quite out of my depth in the new Mendelism of Hogben and Haldane . . . He [HOGBEN] refers too kindly to a thirty year old paper of mine [GARROD's 1902 paper]. It is curious to look back to the old Bateson-Weldon controversies and the position of Mendelism today."

Although reference by geneticists to GARROD's work on inherited metabolic diseases was initially sparse, there was an early and notable exception. SEWALL WRIGHT, who had begun his work on the coat color of guinea pigs in WILLIAM E. CASTLE's department at Harvard and who was to become one of the world's leading population geneticists, became aware of GARROD's work through reading BATESON's *Mendel's Principles of Heredity,* published in 1909, although he did not refer to GARROD when he wrote his Ph.D. thesis at Harvard in 1916. However, by the time WRIGHT took up his position in the Department of Zoology at the University of Chicago in 1929, he promptly introduced his students to a course on "physiological genetics." This consisted of 30 lectures, three of which were devoted to ARCHIBALD GARROD and inborn errors of metabolism (PROVINE 1986, p. 172).

T. H. MORGAN was rather less interested than WRIGHT in biochemical aspects of gene action and, as late as 1934, in delivering his Nobel lecture on "The Relation of Genetics to Physiology and Medicine" (MORGAN 1934) to a largely medical audience, did not refer to GARROD's work. MORGAN was preoccupied more with genetic linkage than with the physiology of gene action, and he clearly perceived the relevance of linkage analysis to human disease: "Even the phenomenon of linkage may some day be helpful in [medical] diagnosis . . . There can be little doubt that there will, in time, be discovered hundreds of linkages and some of these, we may anticipate, will tie together visible and invisible hereditary characteristics."

It was probably GEORGE W. BEADLE who brought GARROD to the attention of geneticists with his generous references to GARROD in his 1958 Nobel lecture (BEADLE 1959): "In this long round about first in Drosophila and then in Neurospora we had rediscovered what Garrod had seen so clearly so many years before." He even suggested that it was GARROD who first proposed a direct relation between genes and enzymes. This was not quite true. The enunciation of the one gene-one enzyme hypothesis by BEADLE and TATUM followed from their experiments on nutritional mutants in Neurospora. Despite some legitimate skepticism on the part of DELBRÜCK and also LEDERBERG (1956), this concept proved to be of

enduring importance and ushered in a new field, biochemical genetics. In his Nobel lecture BEADLE expressed regret that he had been tardy in recognizing the importance of GARROD's work, although BEADLE had first referred to GARROD in 1939 in a lecture at the Seventh International Congress of Genetics, and again in 1941, when he gave a paper on Drosophila at a meeting of the American Association for the Advancement of Science (BEADLE and TATUM 1941).

HALDANE, who had long pondered the nature of gene action, certainly since 1920 when he gave a paper to the Oxford University Junior Science Club entitled "Some Recent Work on Heredity," made no evident recorded reference to GARROD until 1937 when, in a commemorative volume of essays in honor of the 75th birthday of GOWLAND HOPKINS, he accorded GARROD his rightful place as one of the pioneers of biochemical genetics (HALDANE 1937). It was another five years before HALDANE would refer to him again, at least in print.

HALDANE was appointed geneticist to the John Innes Horticultural Research Station in 1927 and became a champion of the work of MURIEL WHELDALE and ROSE SCOTT-MONCRIEF on the biosynthetic pathways of the anthocyanin pigments of plants. Whether they discussed GARROD's highly relevant work on metabolic pathways is not known, but these authors never referred to GARROD and his work; neither did BEADLE remember talking about GARROD when he visited HALDANE at the Institute in 1936, six years before the publication of *New Paths in Genetics* (HALDANE 1942).

In 1909 GARROD had postulated that the metabolic abnormality in alkaptonuria was an inherited deficiency of an enzyme that in normal individuals split the benzene ring of homogentisic acid. This hypothesis was finally proved in 1958, 22 years after GARROD's death, when BERT LA DU and his colleagues (1958) demonstrated the absence of an enzyme, homogentisic acid oxidase, in the liver of a patient with the disease.

ARCHIBALD GARROD will not be forgotten; the biological truths that he uncovered will endure. His role in the development of the field of biochemical genetics is secure. For those in medicine, his life represents the best of clinical investigation, a subject desperately in need of resuscitation and modern interpretation. The extension of his ideas, based on emerging genetic knowledge, to the diagnosis and prevention of human disease is already apparent and will take on even more importance as the map of the human genome unfolds. The twenty-first century, soon to be upon us, will continue to build on GARROD's pioneering thoughts; patients and medical education will be the beneficiaries of the remarkable insights of this physician-scientist who was also a reluctant geneticist (BEARN 1993).

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