Archibald Edward Garrod and alcaptonuria: "Inborn errors of metabolism" revisited

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Archibald Edward Garrod (1857–1936) had a unique role in the history of medical biochemistry. Early in his career, he was recognized by the Royal Society of Medicine[1] for his elucidation of the disorder alcaptonuria and the resultant demonstration of the special relationship between biochemistry, genetics, and their close overlap in the practice of medicine.[1] Garrod showed great interest in genetics even as a youth when he published "The Tiger."[2] This brief work described in simple language the genetic significance of the interspecies mating of a tiger and a lion, suggesting the transmission of hereditary characteristics: "There has been an instance of a lion being the father and a tigress the mother of cubs … [that] had the heads of the lion but the tigerine stripes on the body …."[2]

The alcaptonuria study was the main interest of Garrod when, in 1892, he was appointed Assistant Physician in the Hospital for Sick Children in London. Keying off his sense that urine provided especially useful biological material for diagnostic purposes, he focused on the "black urine" of the children ultimately recognized to have alcaptonuria. In his book, The Inborn Errors of Metabolism,[3] Garrod considered alcaptonuria as an "inborn error of metabolism" after the manner of diabetes and gout, where "inborn" meant "hereditary," although he also clarified the biochemical and distinctive clinical features of the disorder: "Of inborn errors of metabolism, alcaptonuria … attracts attention because an infant stains its clothing or the urine has a peculiar appearance. As the years go on, the cartilages become blackened, giving a blue tint to the hollows of the ears, brown marks develop on the conjunctivae, and there is a great tendency to osteoarthritic and osseous lesions …. Homogentisic acid, the excretion of which is the essential feature of alcaptonuria, was isolated, analyzed, and fully investigated by Wolkow and Baumann … [in a work] published in 1801 …."[3] Garrod continues: "… the administration of tyrosine by mouth to … an alcaptonuric subject … caused a very conspicuous increase of the output of homogentisic acid …. A corresponding increase follows an augmented intake of protein food, and especially of such proteins that are unusually rich in the aromatic fractions … the tyrosine and phenylalanine of proteins are the only parent substances of the alcapton acid [homogentisic acid] …. It will be obvious … that the error of metabolism, which is the basis of alcaptonuria, is a failure to deal with the aromatic fractions of proteins …. It is an unquestionable fact that the great majority of aromatic compounds, when introduced into the human organism, escape with their benzene ring intact and are excreted in the urine …. Not so tyrosine and phenylalanine, which are in no sense foreign substances, but important constituents of proteins, for these suffer disintegration of the aromatic nucleus and are completely destroyed …."[3]

Garrod believed that the human organism does not suffer from a disease when there is homeostasis of "metabolism" and "catabolism," that is, when there is a stable equilibrium among the different enzymatic reactions. He considered that properly balanced enzymatic reactions were fundamental to having "good" or healthy chemistry.[3] Thus, he says regarding alcaptonuria: "The anomaly locates the error in the penultimate stage of the catabolism of the aromatic protein fractions, which is in accord with the fact that both exogenous and endogenous tyrosine and phenylalanine contribute to the excreted homogentisic acid in alcaptonuria. We may further conceive that the splitting of the benzene ring of homogentisic acid in normal metabolism is the work of a special enzyme [and] that in congenital alcaptonuria this enzyme is wanting, while in disease its working may be partially or even completely inhibited."[3]

In 1901, Garrod gave the Croonian Lecture[4] to the Royal Society of Medicine. In this milestone in the field of genetics, he ascribed direct responsibility to the consanguineous parents for the alcaptonuria in their children without his having had any knowledge of Mendelian genetics. "It is evident … that the proportion of alcaptonuric families and individuals who are the offspring of first cousins is remarkably high, and, on the other hand, it is equally clear that only a minute proportion of the children of such unions are alcaptonuric … there is no reason to suppose that mere consanguinity of parents can originate such a condition as alcaptonuria in their offspring, and we must rather seek an explanation in some peculiarity of the parents, which remain latent for generations, but which has the best chance of asserting itself in the offspring of the union of two members of a family in which it is transmitted … it is not the mating of first cousins in general but of those who came of particular stocks that tends to induce the development of alcaptonuria in the offspring. For example, if a man inherits the tendency on his father's side his union with one of his maternal first cousins will be no more liable to result in alcaptonuric offspring than his marriage with one who is in no way related to him by blood. On the other hand, if member of two families who both inherit the strain should intermarry the liability to alcaptonuria in the offspring will be as great as from the union of two members of either family, and it is only to be expected that the peculiarity will also manifest itself in the children of parents who are not related …."[4]

As part of an ongoing project to celebrate the history of medical genetics, the authors are pleased to remind our colleagues in genetics, and in medicine in general, of the creative insights and pioneering work of Archibald Edward Garrod.

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