The centenary of Garrod's Croonian lectures

David J Weatherall

ABSTRACT – Archibald Garrod's Croonian lectures, Inborn errors of metabolism, were delivered at the Royal College of Physicians in June 1908. Although their significance remained dormant for many years, and is still not fully appreciated, they are now recognised as the foundation of medical genetics.

KEY WORDS: Archibald Garrod, medical genetics

Archibald Garrod's Croonian lectures, delivered before the Royal College of Physicians (RCP) in June 1908, published in the *Lancet*, and later as a monograph in 1909,[1] must surely have been among the most important lectures ever delivered to the RCP. As well as defining the new field of medical genetics, they represented a broader view of man's biochemical individuality and the complex interaction between nature and nurture that underlies human disease. Garrod's remarkable insights lay fallow for many years. A second reading of *Inborn errors of metabolism* and his later work *Inborn factors of disease*, however, suggest that there have been few fundamentally new concepts in the field of human genetics since his time.

In this short tribute to Garrod and his work it will only be possible to touch on some aspects of his life and achievements. Those who wish to learn more about this remarkable man are referred to Alick Bearn's excellent biography and to several other works that deal in more detail with various aspects of his work.[2–4]

Garrod's career

Garrod was born in 1857, the fourth son of Sir Alfred Baring Garrod, professor of medicine at King's College Hospital, and the younger brother of Alfred Henry Garrod who, for the two years before his death at the age of 33, was Fullerian Professor of Physiology at the Royal Institution. In 1880, Garrod obtained a first class degree in natural sciences at Oxford and moved to St Bartholomew's Hospital for his clinical training. After a variety of junior hospital posts he settled down at Bart's where he was appointed to assistant physician in 1903, and later, at the age of 55, as a full consultant physician to the hospital. In 1910, like his father and brother before him, Garrod was elected Fellow of the Royal Society. The fact that he was not appointed as a senior physician until the age of 55, and two years after he became an FRS, suggests that either competition was particularly fierce at Bart's at that time or, as seems more likely, his colleagues did not fully appreciate the talents of this unusual physician–scientist whose thinking was so many years ahead of its time. In 1919, he was appointed as the first director of the newly formed medical unit at Barts. Shortly after, he moved to Oxford to succeed William Osler as Regius Professor of Medicine (Fig 1). He retired seven years later and died in 1936.

David J Weatherall FRS, Regius Professor of Medicine Emeritus, University of Oxford

Clin Med 2008;8:309–11

Inborn errors of metabolism

Garrod's interest in biochemistry was fostered by his early association and friendship with Frederick Gowland Hopkins his co-author on a number of papers on the significance of porphyrins in the urine. His work on biochemical individuality was first stimulated by observations on patients with alkaptonuria. He published his first descriptions of the occurrence of this disease in siblings in 1899 and 1901,[5,6] the second paper emphasising the frequency of consanguinity in their parents. Although at first he did not appreciate the genetic significance of these findings, William Bateson, one of the leading protagonists of

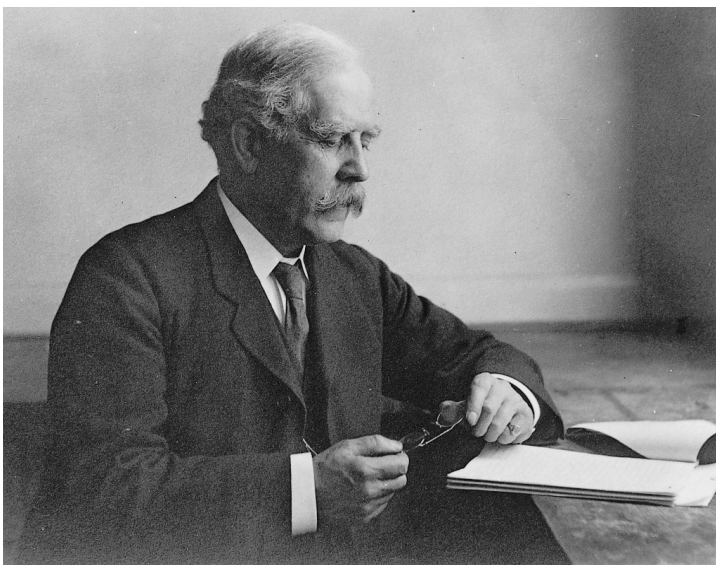

Fig 1. Archibald Garrod during his period as Regius Professor of Medicine at Oxford. Reproduced with permission of National Portrait Gallery, London.

Mendel's work at the time, heard about them and corresponded with Garrod, pointing out that they were just what might be expected in a disease that had a recessive form of inheritance. Garrod included Bateson's interpretation of his work in a later paper 'The incidence of alkaptonuria: a study of chemical individuality' published in the *Lancet* in 1902.[7]

Garrod continued to extend his work on alkaptonuria, realising that homogentistic acid in the urine of patients with this condition is a normal intermediate in the breakdown of phenylalanine and tyrosine, and concluding that in alkaptonuria the failure of its further degradation must result from the absence of an enzyme required to cleave its benzene ring. He also extended his interest in inborn errors, adding cystinuria, pentosuria and albinism to the list. This work culminated in his 1908 Croonian lectures to the RCP and his later monograph.

Garrod's later work and thinking further developed the theme that individual variability and response to disease reflects biochemical diversity which must, in turn, be related to evolutionary adaptation. These ideas were summarised in his second book, *Inborn factors of disease*, published in 1931.[8] After a prologue on the history of doctrines of diathesis the first part is a summary of his ideas about the chemical basis of individuality, the possible role of evolution in modifying disease susceptibility, and the inheritance of what he calls 'morbid liabilities'. The second part speculates on how common diseases, including communicable disease, might be modified by differences in individual susceptibility. The brief epilogue ends with these words:

> *It might be claimed that what used to be spoken of as a diathesis is nothing else but chemical individuality. But to our chemical individualities are due our chemical merits as well as our chemical shortcomings; and it is more clearly true to say that the factors which confer upon us our predispositions to, and immunities from, the various mishaps which are spoken of as diseases, are inherent in our very chemical structure; and even in the molecular groupings which confer upon us our individualities, and which went into the making of the chromosomes from which we sprang.*

Recognition

Perhaps it is not surprising that Garrod's remarkable insights went largely unnoticed during the years after they were published. At the time of Garrod's seminal observations, genetics was in a state of flux, with bitter arguments between biometricians and Mendelians; it was only much later that the work of RA Fisher and others clarified the distinction between monogenic and multigenic inheritance. Garrod was not interested in these disputes and indeed the word 'gene' does not appear in any of his writing. Occasionally, he uses the word 'factor' or even 'sport' but, with the exception of quoting Bateson's genetic interpretation of his families, he never made any attempt to analyse his findings in the light of the developing science of genetics. Yet his remarkable insights and his concept of biochemical individuality are at the heart of genetics in the 20th century.

Many years later, the elegant studies of Beadle and Tattum on the bread mould Neurospora demonstrated that the primary action of a gene is to direct the production of a specific protein, in this case an enzyme. In a lecture delivered in Stockholm in 1958 on the occasion of the award of the Nobel Prize in Medicine to Beadle and Tattum, Beadle described how his earlier work on eye pigments in the fruit fly led to the experiments with Tattum on Neurospora and how, in both these cases, it was possible to generate a series of biochemical mutants, exactly of the type originally envisaged by Garrod to explain the inborn errors of metabolism in man. In his acceptance speech tribute to Garrod Beadle remarked, 'in this long and roundabout way, first in Drosophila and now in Neurospora, we had rediscovered what Garrod had seen so clearly so many years before'.[9] Yet, when *Inborn factors of disease* was reprinted in an edition edited by Charles Scriver and Barton Childs in 1989,[10] it sold only a handful of copies and received no reviews. As pointed out by Garrod's biographer,[2] it was not until 1984, 76 years after Garrod's lectures, that a Croonian lecture, given by the present author, was devoted to medical genetics.

It is surprising that the seminal role that Garrod played in the development of human and medical genetics is still only truly appreciated by some of those who have specialised in the field and, apparently, not by a broader audience of biologists and physicians.

Garrod's contributions seen in the light of current genetics

Garrod's concept of biochemical individuality as it relates to single-gene disorders has been amply confirmed in the era of molecular genetics. But what is more remarkable, the ideas that he set out in *Inborn factors of disease* are almost identical to those that led to current genome searches for genetic variation that underlies susceptibility or resistance to common diseases, ranging from the devastating infectious killers of the developing countries to the major psychoses. Indeed, it is sobering to reflect that there have been relatively few fundamentally new ideas in human genetics since the early part of the 20th century and the work of Garrod, Fisher, Haldane and a handful of others; it is the remarkable technology of the molecular era that has made it possible to bring them to full fruition.

The RCP should be proud to celebrate the centenary of Garrod's great Croonian lectures, for as well as opening up a completely new field of biological thinking they emphasised the critical importance of the role of physician–scientists, with their unique opportunity to take questions from the bedside into the laboratory. Indeed, he was one of the first genuine physician-scientists and, to encourage young physicians to follow similar careers, was a major force behind William Osler in the establishment of the Association of Physicians of Great Britain and Ireland.

Acknowledgements

Part of this essay is based on Reference 4. I thank Alick Bearn for Fig 1 and the National Portrait Gallery for permission to reproduce it, and Liz Rose for her help in the preparation of this essay.

References

1 Garrod AE. *Inborn errors of metabolism*. Oxford: Oxford University Press, 1909.
2 Bearn AG. *Archibald Garrod and the individuality of man*. Oxford: Clarendon Press, 1993.
3 Bearn AG, Miller ED. Archibald Garrod and the development of the concept of inborn errors of metabolism. *Bull Hist Med* 1979;53:315–28.
4 Weatherall DJ. *The role of nature and nurture in common diseases. Garrod's legacy*. London: Royal College of Physicians, 1992.
5 Garrod AE. A contribution to the study of alkaptonuria. *Med-chir Trans* 1899;82:369–94.
6 Garrod AE. About alkaptonuria. *Lancet* 1901;ii:1484–6.
7 Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. *Lancet* 1902;ii:1616–20.
8 Garrod AE. *The inborn factors of disease*. Oxford: Oxford University Press, 1931.
9 Beadle GW. Genes and chemical reactions in *Neurospora*. Nobel lecture, 11 December 1958. In: *Nobel lectures, physiology or medicine 1942–1962*. Amsterdam: Elsevier, 1964:587–97.
10 Scriver CR, Childs B (eds). *Garrod's inborn factors of disease*. Oxford: Oxford University Press, 1989.