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Special article

Archibald Edward Garrod: the physician father of biochemistry

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The life and scientific activity

The authors briefly describe the life and scientific activity of Archibald Edward Garrod (Fig. 1) who is recognized as "the father of biochemistry" by the Royal Society of Medicine. The basis for this recognition is his study of the disorder alcaptonuria, which he discovered and described in his book *Inborn Errors of Metabolism*. In this book, he emphasized the interrelationship between biochemistry and genetics, and that these 2 disciplines are not 2 distinct entities but are closely related in the practice of medicine [1-4].

Archibald Edward Garrod was born on 25 November 1857 in London, the son of Alfred Baring Garrod and Elizabeth Ann Colchester. He grew up in the time when the discipline of medicine was considered an "elite" discipline and only "little" men worked as physicians. His father was a prominent physician who is remembered as the discoverer of the difference between "rheumatic gout" (which involves no increase in uric acid) and "real gout" (which involves an increase in uric acid). Alfred died in 1907 after writing 2 important books: *The Essentials of Material Medica, Therapeutics, and the Pharmacopoeia* and *The Nature and Treatment of Gout and Rheumatic Gout*.

Archibald was raised in an environment that valued science. Alfred's strong personality and cultural activities influenced Archibald's studies and thinking; Archibald was also influenced by his brother Alfred Henry's cultural activities. Alfred Henry was interested in the natural sciences and was a Fellow of the Royal Society of Medicine and an editor of the journal *Nature*. Alfred Henry is remembered for his studies on blood pressure and the use of the sphygmograph, and on the regulation of body temperature in humans.

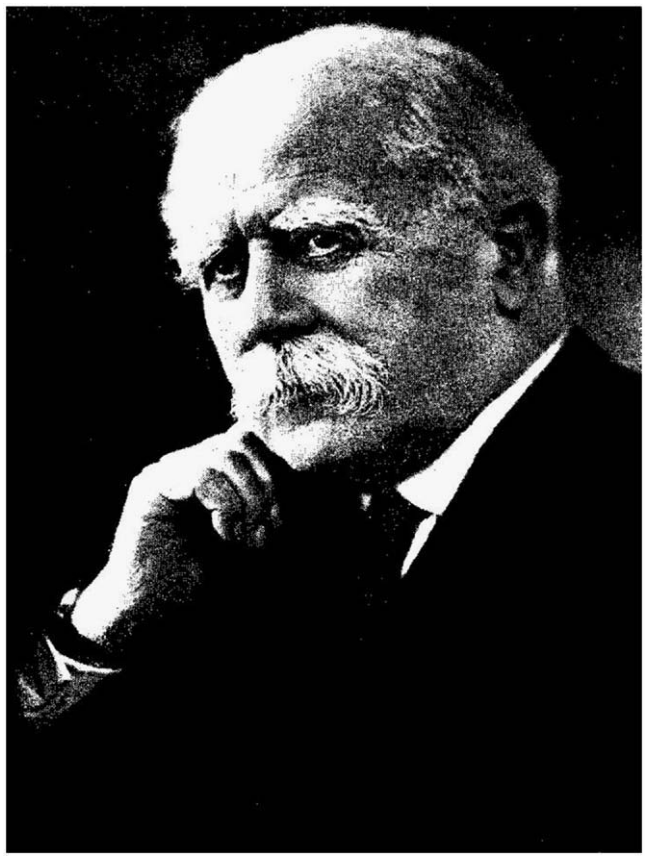

Fig. 1. Archibald Edward Garrod (from *Inborn errors of Metabolism*).

Sir Francis Galton, a cousin of Charles Darwin, also influenced Archibald's scientific work through his study of heredity, published as *Hereditary Genius*, which discusses famous families and the role of heredity in their development. At a young age, Archibald published *The Tiger* in which he describes in simple language the genetic combination of the unusual coupling between a tiger and a lion. From his words:

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"… There has been an instance of a lion being the father and a tigeress the mother of cubs … the cubs had the head of the lion but the tigerine stripes on the body. The lion-tigers before mentioned are not the only animals of that kind that have ever existed…."

In January 1873, when he was 15 years old, Garrod attended Marlborough College in Wiltshire as a pupil at Littlefield House where he studied with Sir James Gilmore, a famous student of mathematics, and Frederic William Farrar, the school's director. These 2 teachers encouraged him to follow his interests in natural science at a time when the classics were considered far more important than natural science. Supported by his teachers, in 1875, Garrod received 2 prizes: the Stanton Prize from the School of Physics and the Clark Prize from the School of Geography.

In 1876, Garrod began his studies at Christ Church College at Oxford University, which awarded him the degree in chemical studies from the School of the Natural Sciences in 1880. Thus began his interest in chemistry, which formed the base for his later studies in medicine and for which he was supported by Augustus George Vernon Harcourt, Fellow of the Royal Society of Medicine.

In 1880, Garrod began his medical career following his belief in the interrelationship between chemistry and medicine. He began work as a physician at the Royal Hospital of St Bartholomew in London, where he compared his innovative ideas with the more conservative ideas of important scientists such as Samuel Jones Gee, the discoverer of celiac disease, and Reginald Southey, the inventor of the "Southey tube," which was used to treat edema (called *dropsy* at the time).

Garrod had a brilliant medical career. In 1881, he won the Junior Scholarship Prize. In 1884, he won the Brockenbury Scholarship in Medicine; and he became a Fellow of the Royal College of Surgeons. In 1885, he was awarded the degree of Bachelor of Medicine and Bachelor of Surgery from the University of Oxford. Garrod became interested in laryngoscopy after reading the 1885 book by Arthur Schnitzler and Leopold Schrotter titled *An Introduction to Use of the Laringoscope*. Garrod became Vice President of the Section of Laryngoscopy of the Royal Medical and Chirurgical Society. In 1885, Garrod also became a Fellow of the Royal College of Physicians.

In 1890, Archibald wrote "A treatise on rheumatism and rheumatoid arthritis." He developed over the next 10 years an interest in rheumatic diseases, which he published with Hunt Cooke as "An attempt to determine the frequency of rheumatic family histories amongst non-rheumatic patients." This work revealed Garrod's developing interest in the influence of heredity on disease.

In 1892, Garrod was appointed Assistant Physician in the Hospital for Sick Children in London, where he began to study children's diseases at the time that pediatrics was becoming recognized as a specific discipline within medicine. From the words of Robert Hutchison: "… His special interest was in biochemistry … particularly rare metabolic disorders and he got excited when he came across a case of alkaptonuria or porphyrinuria…." When Garrod was invited to give a lecture to the Abernethian Society in 1899, he chose as his subject "Some clinical aspects of children's disease" because "… children cannot fail to appeal strongly to your sympathies … whose diseases cannot be ascribed to any fault of their own, but are too frequently attributable to the ignorance and even neglect of their elders…." During these years, Garrod developed a special interest in the chemical changes accompanying human disorders, in particular, disorders affecting children. He believed that urine provides more useful biological material for diagnosis, a belief that led to his studies on alcaptonuria or "black urine," which he discovered.

Garrod's writing about alcaptonuria in his book titled *The Inborn Errors of Metabolism* is instructive. "… Of inborn errors of metabolism alcaptonuria is that of which we know most, and from the study of which most has been learnt. In early life … 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 conjunctive, and there is a great tendency to osteo-arthritic and osseous lesions.… When freshly passed the urine of an alcaptonuric seldom exhibits any abnormality of tint, but it soon begins to darken in contact with the air.… Our knowledge of alcaptonuria is dated from the year 1858, in which year Bödeker detected, in the urine of a patient with glycosuria, a second reducing substance, not a sugar, to which, on account of its behaviour towards alkalies, he assigned the name of 'alkapton,' a bilingual word derived from alkali and κάπτειν. However, indications of the anomaly may be detected in much earlier medical writings. Thus there can be no doubt that the case of an infant who passed black urine, described by Alexander Marcet in 1823, was of this nature. It is true that Marcet knew nothing of the reducing properties of the urine, but he describes accurately its darkening in colour on standing, the staining of napkins, and the effect of the addition of an alkali; and he mentions that the condition was present from the earliest days of the child's life. Until the early years of the nineteenth century no distinction was drawn in medical writings between urines which were black when passed and such as darkened on exposure to air, but it is difficult to suggest any other diagnosis than that of alcaptonuria for some cases referred to in works of the sixteenth and seventeenth centuries, such as that mentioned by G.A. Scribonius (in 1584) of a schoolboy who, although he enjoyed good health, continuously excreted black urine, and that cited by Schenck (in 1609) of a monk who exhibited a similar peculiarity and stated that he had done so all his life. The most interesting record of this kind is to be found in the work of Zacutus Lusitanus, published in 1649. The patient was a boy who passed black urine and who, at the age of fourteen years, was submitted to a drastic course of treatment which had for its aim the

subduing of the fiery heat of his viscera, which was supposed to bring about the condition in question by charring and blackening his bile. Among the measures prescribed were bleedings, purgation, baths, a cold and watery diet, and drugs galore. None of these had any obvious effect, and eventually the patient, who tired of the futile and superfluous therapy, resolved to let things take their natural course. None of the predicted evils ensued, he married, begat a large family, and lived a long and healthy life, always passing urine black as ink..… The substance which Bödeker isolated from the urine of his patient, and which he called 'alkapton,' contained nitrogen and was obviously an impure material. In some cases afterwards recorded the abnormal constituent was thought to be pyrocatechin and in others protocatechuic acid. Marshall obtained from the urine of his patient a substance which he named glycosuric acid, and R. Kirk … isolated an acid which he called uroleucic acid..… There are no sufficient grounds for supposing that the reducing substances present in these earlier cases were different from that found in all the more recent ones … has been possible the presence of homogentisic acid has since been demonstrated..… Homogentisic acid, the excretion of which is the essential feature of the alcaptonuria, was isolated, analysed, and fully investigated by Wolkow and Baumann, as is set forth in their classical paper, published in 1801, some years later than the investigations of Marshall and Kirk. It was shown to have the empirical formula $C_8H_8O_4$ … its constitution is that of *para*-dioxy-benzene-acetic acid (hydroquinone acetic acid)..… In many accounts of alcaptonuria the statement will be found that in some cases there has been present in the urine, in addition to homogentisic acid, a second acid possessed of similar properties-viz. uroleucic acid, and that this substance is probably hydroquinone α-lactic acid..… It will be remembered that the name of uroleucic acid was assigned by Kirk to the material which he isolated from the urine of his patient at the time before homogentisic acid was known. The late Dr. Kirk never claimed that this was a second distinct alcapton acid, and, indeed, in a letter to me he expressed his opinion that his uroleucic acid was merely impure homogentisic acid..… Moreover, when, in 1902, I was enabled by the kindness of Dr. Kirk to examine fresh specimens of the urine of his patients, much homogentisic acid was obtained from them, but there was no indication of the presence of a second alcapton acid … no indication of the presence of uroleucic acid has been found in any of the alcapton urines since described. Therefore the conclusion appears to be justified that no sufficient evidence is forthcoming of the occurrence in some alcapton urines of a second abnormal acid (uroleucic acid)..… Seeing that there is no evidence that synthesis of the benzene ring ever occurs in the animal economy, Wolkow and Baumann looked to the proteins of the food and tissues as the most likely sources of the alcapton acid, and to the aromatic fractions which proteins contain-viz. tyrosin and phenylalanine as its special precursors. This conjecture was shown to be correct by the result of the administration of tyrosin by the mouth to their alcaptonuric subject. Such administration 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 as are unusually rich in the aromatic fractions..… The yield of alcapton acid after feeding with tyrosin or phenylalanine varies with the mode of administration, and when small doses are given at short intervals, instead of a single large dose, the output is practically quantitative..… To sum up, it would appear that the tyrosin and phenylalanine of proteins are the only parent substances of the alcapton acid … successive reduction and oxidation were known to be brought about by bacterial action, Wolkow and Baumann suggested that it might have its seat in the intestine of alcaptonurics, being there brought about under the influence of a rare specific micro-organism. Nowadays this infective theory, which was at one time widely accepted, has been completely abandoned, for it has been abundantly disproved..… Albrecht was the first to suggest that alcaptonuria is a cause of ochronosis … in recent years … that almost all, if not all, alcaptonurics who reach middle life develop ochronosis … on the other hand, alcaptonuria is not the only cause of ochronosis..… The clinical picture of ochronosis is characteristic … the signs are singularly uniform, but naturally are more extensive and pronounced in cases of long standing … one of the earliest signs is a blue coloration of the ears, first of the concha and anti helix and later of the tragus and anti tragus also. To the touch the blackened aural cartilages feel unduly rigid. Another early sign is the appearance of triangular brown patches upon the sclerotics, with their bases towards the corneae, and the sclerotics may acquire a uniform grey tint … the nose may appear blue, and a butterfly-shaped brown pigmentation of the skin of the face may appear. In the hands there may be a blue tint of the knuckles, from staining of the tendons, and rarely brown pigmentation of the thenar and hypothenar eminences and even of the nails..… There is seen a selective staining of the tissues, of a deep brown or black. The cartilages and fibrocartilages are the seats of election, and the staining of the tracheal rings is very noticeable, as also is the blackness of the articular cartilages and intervertebral discs … pigmentation are seen in the endocardium, and in the intima of the arteries wherever there is any atheromatous change. The pigmentation of the skin in advanced cases has already been described. Staining in the kidneys suggests an excretion of the pigment by these glands." Moreover, Garrod continues to explain his theory of the alcaptonuria: "It will be obvious, from all that has gone before, that the error of metabolism which is at the back of alcaptonuria is a failure to deal with the aromatic fractions of proteins … and those of the tissues are implicated in the error. … 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 in combination with sulphuric acid, as aromatic sulphates, or with glycocoll, as the acids of the hippuric group. Not so tyrosin 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.… Hence it would appear that normal serum of men or animals contains a ferment which has the power of destroying homogentisic acid, probably with formation of acetone, whereas this ferment is not present in the serum of alcaptonurics. The question which calls for consideration is whether in alcaptonuria the failure to deal with tyrosin and phenylalanine is or is not complete … the failure to deal with the aromatic fractions of proteins in the ordinary way is complete.… Two explanations are possible of the fact that alcaptonurics excrete homogentisic acid whereas normal persons do not. Either the alcapton acid is a strictly abnormal product formed by a perverted metabolism of tyrosin and phenylalanine, or it is an intermediate product of normal metabolism which in alcaptonurics escapes further change. It may be premised that the behaviour of homogentisic acid in the organism is rather that of a normal product than that of an interloper.… As an acid, homogentisic acid is in part combined with ammonia.… Several observers have obtained evidence of an increased excretion of ammonia by alcaptonurics … is evident that homogentisic acid is a member of that small group of aromatic compounds of which the benzene ring is broken down in their passage through the body … in these respects it behaves as a normal intermediate product might be expected to do … the failure to destroy homogentisic acid is undoubtedly a feature of alcaptonuria … the assumption that the alcaptonuric, who alone has the power of forming homogentisic acid, is also exceptional in having no power of destroying it when formed. The impaired destruction of the alcapton acid which results from certain morbid conditions has interesting bearings upon the question of temporary or intermittent alcaptonuria.… A temporary or intermittent excretion of homogentisic acid seems more compatible with the theory that it is a normal metabolic product than with the opposite theory.… Any compound, which represents a link in the chain should, on the one hand, be destroyed in the normal organism, as tyrosin and homogentisic acid are, and, on the other hand, should increase the output of homogentisic acid by alcaptonurics.… Where the alcaptonuric differs from the normal individual is in having no power of destroying homogentisic acid when formed.… This conception of 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 tyrosin 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, that in congenital alcaptonuria this enzyme is wanting, whilst in disease its working may be partially or even completely inhibited."

In January 1903, Garrod became Assistant Physician at St Bartholomew's Hospital, where he was also Lecturer for Chemical Pathology until he went to Oxford University in 1919. His personal and scientific contributions were recognized by William Osler, who invited him to become an editor in 1907 of the *Quarterly Journal of Medicine*. In 1909, Garrod became a Fellow of the Council of the Royal College of Physicians; and in 1910, he became a Fellow of the Royal Society of Medicine. He remained active within these organizations until he retired in 1936 because of ill health.

On 4 August 1914, Garrod joined the armed forces. For the first 15 months of the war, he served with the rank of major as a general medical consultant at the First London General Hospital in Camberwell. In November 1915, he left England and sailed for Malta to join the Mediterranean forces as a temporary colonel in the Army Medical Service. On this island, Garrod studied and described a syndrome called *soldier's heart*. Garrod noted that soldiers undergoing prolonged physical and mental strain experienced lassitude, weakness, and a feeling of faintness. He observed that many of the men with the so-called soldier's heart were short of breath and often developed a slight enlargement of the right side of the heart, as judged by percussion.

On 16 December 1916, the University of Malta conferred the degree of MD, honoris causa, on Garrod and his colleagues Charles Balance, Walter Thorburn, and Howard Tooth in recognition of their professional eminence and the important work they rendered during the war.

In January 1920, Garrod received a letter from Arthur Thomson, Professor of Anatomy of Oxford University. From the original letter: "… In complete agreement with my colleagues Dreyer [Georges Dreyer, Professor of Pathology], Sherrington [Charles Sherrington, Professor of Physiology], and Gunn [IA Gunn, Professor of Pharmacology], J write you to ascertain whether you would be prepared to accept the Regius professorship here if invited by the Prime Minister.… We hope you will give the matter your favourable consideration and that you will send here a telegram on Monday with your decision." Garrod accepted the invitation and received on March 2 the following answer from Ernest Evans, the Prime Minister's Secretary: "… the King has been pleased to approve of your appointment to be Regius Professor of Medicine in the University of Oxford." Archibald continued as Regius Professor until he retired from the position at the age of 63 years in December 1927. At Oxford, Garrod continued his studies of the biochemical and chemical characterization of human diseases. In 1927, he became an Honorary Fellow of the British Pediatric Association; in 1928, he became an Honorary Fellow of both the Association of American Physicians and the British Association of Dermatology and Syphilology; and in March 1932, the Historical Section of the Royal Society of Medicine held a meeting in Garrod's honor on the history of the introduction of biochemistry into medicine. Here, Gowland Hopkins, President of the Royal Society, emphasized the debt that the field of biochemistry owed to medicine. Deciding who deserved the title of "father of biochemistry," Hopkins said, was difficult; but he had

decided in the end that so complex a subject deserved 2: Justus Liebig and Sir Archibald Garrod.

At 76 years of age, Garrod retained an acute mind; but he was physically frail and inclined to be irritable. He developed retinal macular degeneration and had angina pectoris and cardiac asthma. Archibald Edward Garrod died at the age of 78 years.

We believe that the best way to remember Archibald Garrod is to repeat the words of Nobel Prize winner George Wells Beadle who, together with Edward Tatum, declared the famous theory called *one gene–one enzyme*: "… I myself am convinced that the one gene–one enzyme concept was the product of gradual evolution beginning with Garrod.… In this long, round about way, first in *Drosophila* and then in *Neurospora*, we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle.… Thus we were able to demonstrate that what Garrod had shown for a few genes and a few chemical reactions in man was true for many genes and many reactions in *Neurospora*."

Inborn errors of metabolism

Garrod's book *Inborn Errors of Metabolism* was dedicated to Frederick Gowland Hopkins and is considered a milestone in the study of biochemistry. In it, Garrod described in detail the biochemical individuality of humans and how metabolic errors and, consequently, diseases are caused by a deficiency in or absence of particular enzymes. We have discussed above Garrod's original research on alcaptonuria, and we include Garrod's own words about his theories on the biochemical individuality of humans: "… As regards the chemical composition of the tissues of living organisms, and the metabolic processes by which those tissues are built up and broken down, the advance has been in the opposite direction, for the progress of bio-chemistry is teaching us that behind a superficial uniformity there exists a diversity which is no less real than that of structure, although far less obvious.… Obviously it is among the highly complex proteins that such specific differences are to be looked for, rather than in the simple end-products of their disintegration.… The existence of chemical individuality follows of necessity from that of chemical specificity, but we should expect the differences between individuals to be still more subtle and difficult of detection.… Upon chemical as upon structural variations the factors which make for evolution have worked and are working.… Even in the normal metabolic processes the working of such influences may be traced, as in the power which the organism possesses of destroying the benzene ring of those aromatic amino-acids which enter into the composition of proteins.… Such compounds require to be rendered innocuous by being combined with sulphuric acid to form aromatic sulphates, or with glycocoll to form the acids of the hippuric group and, so combined, are excreted in the urine … the newly-acquired knowledge of the constitution of proteins and of the part played by enzymes in connexion with the chemical changes brought about within the organism, have profoundly modified our conceptions of the nature of the metabolic processes, and have made it easier to understand how these changes may differ in the various genera and species. It was formerly held that many derangements of metabolism which result from disease were due to a general slackening of the process of oxidation in the tissues. The whole series of catabolic changes was looked upon as a simple combustion, and according as the metabolic fires.… The conception of metabolism in block is giving place to that of metabolism in compartments.… It may well be that the intermediate products formed at the several stages have only momentary existence as such, being subjected to further change almost as soon as they are formed; and that the course of metabolism along any particular path should be pictured as a continuous movement rather than as a series of distinct steps.… All that is known of the course of catabolism tends to show that in such circumstances the intermediate product in being is wont to be excreted as such, rather than that it is further dealt with along abnormal lines … if the conception of metabolism in compartments, under the influence of enzymes, be a correct one, it is far easier to suppose that when, for any reason, the ordinary paths are blocked normal intermediate products are excreted without further change, or that secondary processes which in health play but small parts in metabolism are called into unwonted activity.… To prove the truth of the contention put forward it would be necessary to show that every abnormal product found in the tissues or in the excreta, under morbid conditions, can be ascribed to other causes than the deflexion of the metabolic processes into new and unwonted paths … when an endeavour is made to classify the unusual constituents which are occasionally present in that most important animal excretion, the urine, it is found that there are few of them which cannot be accounted for as intermediate products incompletely burnt, or as exaggeration of traces normally present, if we exclude such as are merely foreign substances absorbed from the alimentary canal or derivatives of these, or are products of bacterial life and action in the intestines or in the tissues. A number of unusual constituents of urine, and of normal constituents also, are derived from the alimentary canal. Thus foreign substances administered in food or as drugs may be excreted unchanged, or may undergo oxidation or reduction in the intestine or after absorption, or again may appear in the urine in combination with products of metabolism.… When other harmful substances … are introduced in abnormal quantities the protective processes are stimulated to unwonted activity.… There is a group of maladies in which metabolic disturbances are by far the most conspicuous features, whereas the structural changes behind them are scanty or even inappreciable. Of such 'diseases of metabolism,' diabetes, gout, and obesity are the most

important.… Quite unlike that of the above metabolic diseases is the course of the anomalies of which I propose to treat, and which may be classed together as inborn errors of metabolism. Some of them are certainly, and all of them are probably, present from birth. The chemical error pursues an even course and shows no tendency to become aggravated as time goes on, and they are little likely to be influenced by any therapeutic measures at our disposal … is tempted to regard them as metabolic sports, the chemical analogues of structural malformations. It is interesting to note that as far back as the earlier years of the nineteenth century, one of them, albinism, was classed by Mansfeldt and by Meckel as a *hemmungsmissbildung* or malformation by arrest.… It may be pointed out that the epithets inborn and congenital are by no means synonymous. Structural abnormalities may be present at birth which owe their origin to intra uterine disease or intra uterine injury and are in no sense developmental errors. Again, an infective disease may be congenital but cannot be inborn. It has merely been acquires in utero. Even true developmental errors are of several distinct kinds. In some there is malposition or transposition of organs, partial or complete; in others doubling of parts or inclusion of twin structures. Some structural anomalies are malformations by excess, such as polydactyly, and some are malformations by defect, such as absence of the middle phalanx of each digit. In one large class, the so-called malformations by arrest, the process of development meets with a check and some portion of the body is left unfinished. To this group belong such abnormalities as hare lip, cleft palate, and spina bifida. No extraneous causes, such as intra uterine injury or disease, can be assigned to the metabolic errors which are under discussion. As far as our present knowledge of them enables us to judge, they result from failure of some step or other in the series of chemical changes which constitute metabolism, and are in this respect most nearly analogous to what are known as malformations by defect.… Almost any structural defect will entail some disorder of function … so conspicuous that it completely overshadows the defect to which it is due.… In the same way beneath each chemical sport there may possibly exist some abnormality of structure, so slight that it has hitherto escaped detection.… Each of the known inborn errors of metabolism manifests itself in one or other of these ways, and this suggests that they are merely the most obvious members of a far larger group, and that not a few other such abnormalities which do not so advertise their presence may well have escaped notice hitherto.… To be harmless is no essential attribute of an inborn metabolic error, but it stands to reason that an abnormality which persists from birth into adult and even to advanced life must be relatively innocuous as such.… When we come to discuss the several known inborn errors of metabolism in more detail it will be seen that in the case of each of them the most probable cause is the congenital lack of some particular enzyme, in the absence of which a step is missed, and some normal metabolic change fails to be brought about."

The Croonian lecture

In 1901, Archibald Garrod gave the Croonian Lecture to the Royal Society of Medicine; this was a milestone for the fields of biochemistry and genetics. In his lecture, Garrod described the direct responsibility of consanguineous mates for some diseases, and the experiences of other scientists, without any knowledge of mendelian genetics. Again, Garrod as a good biochemist demonstrates the genetics of recessive characteristics. From his words: "In a paper read before the Royal Medical and Chirurgical Society in 1901 the present writer pointed out that of four British families in which 11 were congenitally alkaptonuric members no less than three were the offspring of marriages of first cousins who did not themselves exhibit this anomaly.… Dr. Erich Meyer … informs me that … they are first cousins. Dr. H. Ogden states that his patient is the seventh of a family of eight members and that his parents were first cousins. The three eldest children died in infancy; the fifth, a female, has three children, but neither is she nor are they alkaptonuric. There is no record of any other examples in the family. The patient, whose wife is not a blood relation, has three children none of whom are alkaptonuric. Professor Hammarsten states that the parents of an alkaptonuric man,… were first cousins.… Dr. Ewald Stier informs me that the parents of his patient were not related and … that they were not alkaptonuric. Professor Ebstein states that the parents of the child with 'pyrocatechinuria' whose case was investigated by him in conjunction with Dr. Willer in 1875 were not related, but I gather that he would not regard this as an ordinary case of alkaptonuria, the abnormal substance in the urine having been identified as pyrocatechin. Prof. Osler supplies the very interesting information that of two sons of the alkaptonuric man previously described by Dr. Futcher one is alkaptonuric. This is the first known instance of direct transmission of the peculiarity. The parents of the father, who has alkaptonuric brother whose case was recorded by Marshall, were not blood relations.… It will be seen that the results of further inquiries on the continent of Europe and in America confirm the impression derived from the British cases that of alkaptonuric individuals a very large proportion are children of first cousins.… It will be noticed that among the families of parents who do not themselves exhibit the anomaly a proportion corresponding to 60 per cent are the offspring of marriages of first cousins … among 50 patients simultaneously inmates of St. Bartholomew's Hospital there was one whose parents were first cousins. On another occasion one such was found among 100 patients, and there was one child of first cousins among 100 children admitted to my ward at the Hospital for Sick Children. It is evident, on the one hand, that the proportion of alkaptonuric 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 alkaptonuric.… The question of the liability of children of consanguineous marriages to exhibit certain abnormalities or to develop certain diseases

has been much discussed.… There is no reason to suppose that mere consanguinity of parents can originate such a condition as alkaptonuria in their offspring, and we must rather seek an explanation in some peculiarity of the parents, which may 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 come of particular stocks that tends to induce the development of alkaptonuria 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 alkaptonuric offspring than his marriage with one who is in no way related to him by blood. On the other hand, if members of 2 families who both inherit the strain should intermarry the liability to alkaptonuria 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 … a very small proportion of alkaptonurics are the offspring of parents either of whom exhibits the anomaly.… It is difficult to imagine that of twins developed from a single ovum one should be alkaptonuric and the other normal, but this does not necessarily apply to twins developed from separate ova.… Alkaptonuria is merely an alternative mode of metabolism and not a morbid condition … it appears not to have been congenital and continuous but temporary or intermittent.… The mother of seven children, three of whom are alkaptonuric, was convinced that whereas two of her children had been alkaptonuric from the earliest days of life this had not been so with the youngest child in whom she had only noticed the peculiarity from the age of five years. This is specially interesting as supplying a link between the temporary and congenital cases.… If it be a correct inference from the available facts that the individuals of a species do not conform to an absolutely rigid standard of metabolism, but differ slightly in their chemistry as they do in their structure, it is no more surprising that they should occasionally exhibit conspicuous deviations from the specific type of metabolism than that we should meet with such wide departures from the structural uniformity of the species as the presence of supernumerary digits or transposition of the viscera."

List of works by Archibald Edward Garrod

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