ESSAY

Heredity before genetics: a history

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Abstract | Two hundred years ago, biologists did not recognize that there was such a thing as 'heredity'. By the 1830s, however, insights from medicine and agriculture had indicated that something is passed from generation to generation, creating the context for the brilliant advances of Mendel and Darwin. Recent work on the history and philosophy of science has shed light on how seventeenth-, eighteenth- and nineteenth-century thinkers sought to understand similarities between parents and offspring.

The existence of heredity is now so firmly established that it is difficult to imagine a time when we did not realize that there were consistent relations between parents and offspring. But, as little as two centuries ago, the word 'heredity' had no biological meaning. There was no study of heredity for the simple reason that it had not been realized that such a phenomenon existed. For at least 2,000 years, discussions of similarities and differences between offspring and parents were tacked on to more general explanations of the origin of life — 'generation'. This term was used to describe a single, perplexingly complex phenomenon that we would today consider to be a fusion of reproduction, genetics and development. In dealing solely with the 'heredity' side of generation, much of this article is therefore a deliberate anachronism, a focused but partial description that the people whose work it describes would not have recognized[1].

Over the past decade, historians and philosophers of science have shed new light on the sources that enabled Mendel to lay the foundations of genetics, and Darwin to put heredity at the heart of his theory of evolution by natural selection. Three strands of knowledge — science, agricultural practice and medicine — each provided key insights on the road to heredity. This took place in a political and social context, symbolized by the French Revolution of 1789, in which the traditional meaning of 'heredity' — a legal term relating to property and monarchical power — was subject to intense philosophical and practical scrutiny.

Although the three strands of thought that I discuss were not strictly separate, the professionalization of science and medicine, and the different values that were placed on different kinds of knowledge, tended to isolate ideas in each of these fields until the 1830s, when they came together to set the scene for the world-changing breakthroughs of Mendel and Darwin[2].

Earliest thoughts about life

The oldest examples of human figurative art are of the female body or genitalia, and it is generally assumed that they were in some way associated with female fertility[3]. It seems most likely that, until the domestication of animals provided a simple model, humans did not appreciate the link between sexual intercourse and pregnancy, or that both sexes are involved in creating life. Women alone had that power. This supposition is supported by the widespread existence of matrilineal communities in hunter–gatherer societies, and by modern anthropological evidence that the matrilineal Trobriand Islanders of Papua New Guinea had no concept of biological fatherhood (although this suggestion has been contested, it is the case that their word for 'father' means 'my mother's husband')[4].

Whatever the case, for the most recent part of humanity's history — that which has occurred since the rise of civilization — the involvement of both males and females in producing new life has been taken as a given. That did not mean, however, that the two sexes were considered to make complementary contributions, or that there was thought to be any consistent observable relation between parents and offspring. A classic assumption — which persists in much folklore today — turned the apparent prehistoric focus on women on its head, producing a male-centred view. Semen — the only immediately apparent product of copulation — was thought to be 'seed' ('semen' means seed in Greek); parents still talk to children about 'Daddy planting a seed in Mummy's tummy'.

The Ancient Greeks came up with two contrasting views of human generation: Hippocrates argued that each sex produced 'semen', which then intermingled to produce the embryo, whereas Aristotle claimed that the woman provided the 'matter', in the shape of her menstrual blood, with the father's semen providing the 'form', shaping the female contribution in some unknown way. The great physician Galen, whose approach was to dominate European and Arab medicine for around 1,500 years, adopted many of Hippocrates ideas, including his 'two-semen' theory of generation.

Although both the Aristotelian and the Galen–Hippocrates views focused on the mechanisms of how life was formed, they also attempted to explain the similarities and differences between offspring and parents that everyone could notice. The two-semen theory naturally led to a view of generation (and therefore of resemblance) that involved the blending of the parental contributions. Similarly, Aristotle recognized that his male-centred view needed to take account of the role of the female, so he argued that the matter (the female contribution) could affect the form (the male contribution), just as a plant would look different if a seed was grown on different soils. However, neither man put forward a description of anything like 'heredity', because there did not seem to be any consistency in what they observed.

The ideas of Aristotle and Hippocrates dominated Western (including Islamic) ideas about generation for over 1,500 years. On the other side of the planet, Chinese thinking about generation did not try to

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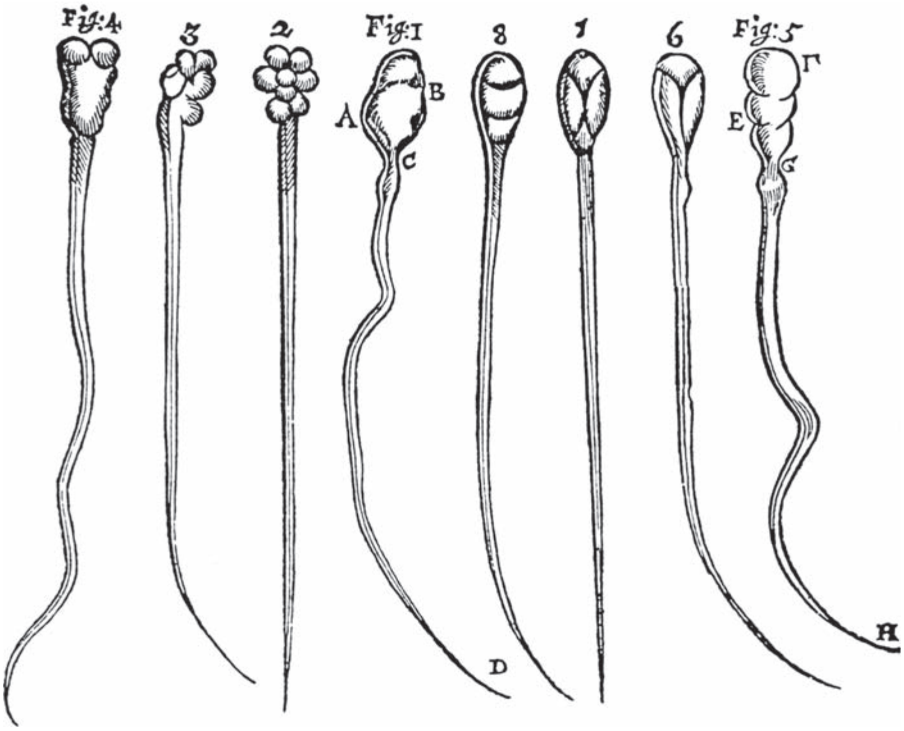

Figure 1 | **Leeuwenhoek's illustration of spermatozoa.** Antoni Leeuwenhoek discovered spermatozoa in 1677, although the name was coined in the 1820s by Karl-Ernst von Baer. Image courtesy of the author © (2006) M. Cobb.

locate functions in structures, but instead focused on the 'generative vitality' of each sex, defined in terms of the energy flows of organ networks[5]. On a world scale, there was little agreement about how generation took place, about the contribution of each sex, or about how and why offspring resembled parents.

Early scientific studies of generation

The first important advance in understanding 'generation' came in the second half of the seventeenth century, through the work of Reinier de Graaf, William Harvey, Francesco Redi, Nicolas Steno and Jan Swammerdam[6]. Using theory, dissection and experimentation, they provided proof that 'like breeds like' in all parts of the macroscopic world (including the difficult case of insects, which everyone, including Harvey, had thought were generated spontaneously), and put forward the theory that all female organisms, including women, produced eggs. A few years later, Antoni Leeuwenhoek rocked the world with his discovery of spermatozoa (FIG. 1) (although they were not called this until the 1820s, by Karl-Ernst von Baer, who was also the first person to actually observe the mammalian egg). All the components were there, but no decisive advance was made.

Surprisingly to the modern eye, no one in the seventeenth century argued that eggs and sperm represented complementary elements that made equivalent contributions to the offspring. Instead, the next 150 years were dominated by either 'ovist' or 'spermist' visions of what eventually became known as 'reproduction' (the term was coined only in 1745) (REF. 7). Each view considered that only one of the two parental components provided the stuff of which new life was made, with the other component being either food (as the spermists saw the egg), or a force that merely 'awoke' the egg (as the ovists saw the spermatozoa).

There were many reasons underlying this apparent scientific dead end. For example, in chickens, the two elements did not seem to be equivalent at all: there was a single enormous egg, which was apparently passive, whereas the 'spermatic animals' were microscopic, incredibly active, and present in mind-boggling numbers. Ultimately, however, the reason that late seventeenth-century thinkers did not realize what to us seems blindingly obvious — that both eggs and sperm make equal contributions to the future offspring — was that there was no compelling evidence to make them appreciate this. Worse, such evidence could (and would) come only from the study of something that, at the time, was not even recognized to exist: consistency in the relations between parents and offspring, or heredity.

The problem was not that thinkers did not look for similarities between the generations, but that they did, and were understandably confused by what they saw. Human families provided striking, highly contradictory and apparently inconsistent evidence — children sometimes looked like one parent, sometimes a mixture of the two, sometimes like neither and sometimes like their grandparents. Harvey perceptively summed up the difficulties in his 1651 work, *De Generatione Animalium* ('*On the Generation of Animals*') (FIG. 2). Harvey mused: "…why should the offspring at one time bear a stronger resemblance to the father, at another to the mother, and, at a third, to progenitors both maternal and paternal, farther removed?" He had no answer, but he had other questions, such as why some birthmarks and moles recur from one generation to the next, whereas others do not.

Finally, Harvey contrasted the pattern that was seen for most characters, which seemed to involve some kind of mixture of the parental types, to that which is seen in the sex of individuals, which in virtually all cases shows no blending at all: "I have frequently wondered how it should happen that the offspring, mixed in so many particulars of its structure or constitution, with the stamp of both parents so obviously upon it, in so many parts, should still escape all mixture in the organs of generation; that it should so uniformly prove either male or female, so very rarely an hermaphrodite."[8] Harvey's string of apparently contradictory examples shows how difficult it was to discern any kind of pattern in the facts of heredity by simply observing a range of human characters.

In a rare experimental study of resemblance, Leeuwenhoek provided yet another example of the way characters appeared in each generation, and added to the prevailing perplexity. Using what could have been a tractable model — rabbits — Leeuwenhoek was surprised to find that a grey male wild rabbit could give rise to only grey offspring. But Leeuwenhoek argued that spermatozoa were the sole source of the future animal, so his strange finding from rabbits became "…a proof enabling me to maintain that the foetus proceeds only from the male semen and that the female only serves to feed and develop it."[9] In other words, there was no relation between both parents and the offspring, but simply between father and offspring, which was represented by the little animal in the male semen. The father was

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grey, so the offspring were inevitably grey, thought Leeuwenhoek.

It is tempting to imagine that if he had done the reciprocal cross, using a grey female wild rabbit, or if he had studied the grandchildren of his grey male, Leeuwenhoek might have paused for thought and the course of science might have been changed. Sadly, given Leeuwenhoek's self-proclaimed stubbornness and his habit of breezily ignoring contradictory evidence[6], it seems much more likely that he would have either discarded his findings or found another explanation that supported his certainty that spermatozoa were the sole contributors to the future organism.

The ovist and spermist visions of generation that dominated eighteenth-century thinking were characterized by the idea of 'pre-formation', whereby the future organism was contained in either the egg or the sperm. To explain why offspring were nevertheless not identical to either parent, thinkers could point to Aristotle's suggestion that plant seeds grew differently depending on soil conditions, although many people felt uncomfortable with this explanation[10]. Similar post-hoc explanations were used to explain the appearance of 'monsters' (offspring with striking birth defects), which seemed to indicate that there was no

Figure 2 | **The frontispiece to Harvey's De Generatione Animalium.** Zeus is shown on the cover of William Harvey's 1651 work, in which he outlined problems in understanding the similarities between parents and offspring. Image courtesy of the author © (2006) M. Cobb.

straightforward relation between parent and offspring, and undermined the great step forward that was made by work on generation in the 1660s, the certainty that 'like breeds like'. Implicit in all this — although it was never stated at the time — was the assumption that, were it not for varied intervening factors, offspring would look just like either their father or their mother. Because there was no discernible pattern to the way those factors affected appearance, no one pursued the matter further.

Eighteenth-century insights

In the first part of the eighteenth century, the question of the reappearance of characters across generations was implicit in the ideas of Linneaus, through his work on plant hybridization, taxonomy and reproduction, and in Antoine-Nicolas Duchesne's presentation of a new variety of strawberry[11,12], but neither man discussed the question explicitly. Surprisingly, neither did Lamarck ('the inheritance of acquired characteristics' is a much later formulation of his ideas)[13].

The most prescient eighteenth-century approach to hereditary phenomena came from Pierre Louis Moreau de Maupertuis, although it had no effect on mainstream thinking at the time. In 1745, Maupertuis used the famous case of a 'white negro' (a black albino child) and put forward a theory of both similarity and development[14]. For Maupertuis, both parents contributed 'particles' to the offspring; if there were too many or too few of one type of particle, a monster could appear. Maupertuis perceptively suggested that the albino child's colouration could be due to 'particles' from an ancestor, or to a change in the particles themselves. This theory was rejected by most of his contemporaries, mainly because Maupertuis ignored the best evidence of the time and dismissed the roles of both eggs and sperm, adopting a version of the Greek atomist idea of 'pangenesis', according to which generative particles existed in all tissues[15].

A few years later, Maupertuis and René-Antoine Ferchault de Réaumur both studied polydactyly (FIG. 3), using families from Germany and Malta, respectively. Decisively, both thinkers looked at the way the character reappeared over the generations — Maupertuis had data from four generations, Réaumur from three. The pattern they observed was clearly not that which was expected by pre-formation (not all offspring were affected), nor was it a one-off phenomenon like a monster. Maupertuis even took a step towards a probabilistic analysis of heredity when he calculated the probability

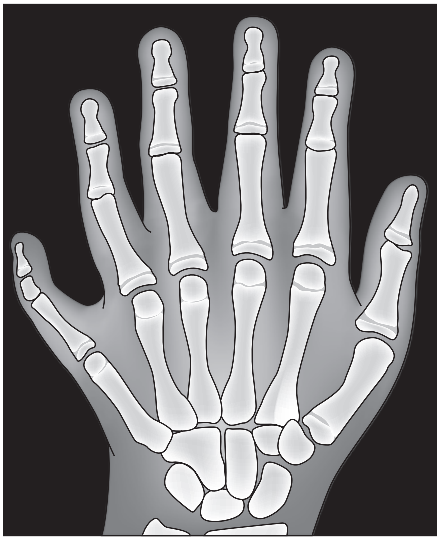

Figure 3 | **Polydactyly.** Maupertuis and Réaumur studied how polydactyly was inherited through the generations.

that polydactyly would not be transmitted over three consecutive generations (the result was a staggering 8×10^{12} to 1) (REF. 16). Like his general ideas about generation, however, Maupertuis's calculation had no impact at the time, and there is no evidence that Mendel, who used a statistical analysis of large data sets, knew of his approach.

Despite such examples, which for us seem extremely telling, by the early years of the nineteenth century, scientific approaches to the study of generation had not revealed that there was such a thing as biological heredity. Indeed, thinkers still did not realize that both sexes contributed equally to the offspring (Réaumur and Bonnet's discovery of aphid parthenogenesis in the 1740s had not helped matters). Even the first person to see the mammalian egg, Ernst von Baer, was a convinced ovist who, in common with many other thinkers of the time, classed spermatozoa as parasitic worms.

In some ways, the scientists who tried to study generation succeeded only in making the reality of biological heredity even more difficult to discern. The multiple and contradictory examples they provided, and the microscopic enigmas that their instruments revealed, were ultimately less informative than the very practical knowledge that had recently been developed in agriculture.

New thinking from breeders

At the heart of agricultural practice is the assumption that, as Thomas Blundeville, an author with an interest in horse breeding, mathematics and navigation, put it

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in 1566: "…it is naturally geven to every beast for the moste parte to engender hys lyke."[17] However, as Blundeville indicated, this was not always the case, and until the seventeenth-century studies on generation, it was not even clear that it applied to all organisms. More surprisingly, until the second half of the eighteenth century, there does not seem to have been any explicit attempt to exploit this phenomenon; selective breeding, in terms of a conscious decision to manipulate the stock of a domesticated organism, was not widespread, nor was it transformed into a theory. Breeders' 'knowledge' that like bred like was partial and entirely heuristic: they were concerned with what worked, not why[18].

Partial insights that seem striking to us were not exploited or used as the starting point for further knowledge. For example, in the second half of the first century, Lucius Junius Moderatus Columella summarized Roman agricultural knowledge in *De Re Rustica* ('*On Rural Matters*'). Problems that were associated with animal breeding take up only a few sentences, although Columella noted that blending of coat colour was typically the case, and the grandsire's coat colour could reappear in the second generation[19]. However, this was not enough to spark his or anyone else's interest.

The difficulty with the breeders' basic assumption that like breeds like was that it was not always true. As Nicholas Russell has pointed out, when seventeenth-century English horse breeders tried to import animals from Arabia, the horses generally failed to flourish and rarely reproduced all the qualities that had made them attractive in the first place. As a result of many such experiences, "…most authors believed that the virtue of horses from exotic locations was only transmissible over generations while they remained in these places."[18] Far from seeing the characters of their animals as having an innate, constitutional basis that could pass from one generation to another, breeders — like Aristotle and other thinkers — accepted that local conditions had a decisive role in shaping characters.

From the seventeenth-century, breeders tended to use the term 'blood' to describe the quality that apparently lay behind the characters of an animal. But, as with a royal 'bloodline', this was a vague, semi-mystical view of the power of an imprecise quality, rather than a recognition of the hereditary transmission of characters. This confusion was translated into practice: eighteenth-century racehorse breeders would not cross two successful racehorses, creating a 'thoroughbred' stock, but would instead cross racing stallions with local mares[18].

During the eighteenth century, however, agricultural breeders in the United Kingdom — in particular, sheep breeders — began to appreciate the power of selection, and to create new, true-breeding lines of animals[20]. The key figure was Robert Bakewell, a sheep breeder from Dishley, near Loughborough, England. In the middle of the century, Bakewell seized on the opportunity that was provided by the growing demand for mutton in a thriving UK economy, to launch a deliberate programme of selective breeding to create a race of sheep that grew more quickly and produced more meat than traditional breeds.

Bakewell's procedure was painstaking and involved scouring the surrounding counties for animals that met some or all of his four criteria: 'beauty', the proportion of edible to non-edible parts, meat quality and growth rate. The key point was that male and female had to be matched, and that the focus was on the development of a herd of animals with similar characteristics, rather than on producing occasional outstanding individuals. This required Bakewell to think in terms of populations — one of the keys to realizing that there is such a thing as heredity.

The aim of Bakewell's work, which was pragmatic and heuristic in approach, was simple: he frankly described his barrel-shaped breed, the New Leicester (FIG. 4), as "…a machine for turning herbage … into money."[20] He claimed that castrated New Leicester rams could be killed for best profit at two years, rather than the four years that was typical of other breeds — an increase in productivity that indicates the effectiveness of his breeding programme.

The financial impact of Bakewell's work was substantial, and he was able to hire out his rams for over £1,000 for a season (an astonishing sum at the time), but the huge cost of maintaining his rigorous selection programme meant that he was perpetually in danger of going into debt (he nearly went bankrupt in 1776). Because of the potential for making large sums of money, visitors came from all over Europe to study Bakewell's amazing man-made sheep, and his equally astonishing breeds of horses, pigs and cattle. Farmers from France, Germany, Russia and Austria all sought to copy his techniques.

The scientific community was less impressed. The president of the Royal Society, Sir Joseph Banks, was not only a leading botanist, but also a major sheep farmer. Banks had tried to introduce the Spanish wool breed of sheep, the Merino, on his farm, but with little success; this failure might explain his suspicions of Bakewell, who he suggested was "…promoting his breed by cunning and impudent means."[20] Neither Bakewell nor Banks, nor anyone else at the time, seem to have realized the profound theoretical implications of Bakewell's breeding programme; the simple fact that he had created a new race that bred true was all that mattered. That, and the money.

Figure 4 | **A New Leicester sheep.** Robert Bakewell's famous barrel-shaped breed. Image taken from an original painting by A. Churchill, kindly provided by the artist © (2006) A. Churchill.

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In the early years of the nineteenth century, following Bakewell's death, the impact of his work led directly to new thinking about heredity. As Roger Wood and Vítězslav Orel have shown[20,21], Bakewell's approach was soon applied to wool production, and led to the introduction of the Merino into Central Europe, in particular through the efforts of Ferdinand Geisslern in Moravia. Brno — the capital of Moravia and known in the nineteenth century as the 'Austrian Manchester' — was a centre for both the textile industry and sheep breeding. Thinkers in the local scientific and agricultural community began to try to understand the new techniques they were using. As early as 1819 they outlined what they called 'genetic laws', such as the fact that grandparental traits could sometimes reappear, just as Columella had noticed nearly 2,000 years earlier. For practical and theoretical reasons, they also addressed an issue that was fascinating plant breeders at the time[22] — the problem of predicting what kind of hybrid would be produced from a cross between two breeds.

Although teetering on the brink of insight, this work did not immediately lead to a great breakthrough in our understanding of heredity. However, it had the enormous virtue of creating an intellectual context in the Brno region that contributed to Mendel's interest in heredity and hybridization. In 1837, the purest expression of this interest was shown by Abbot Napp, who, 6 years later, would welcome Mendel to the Brno monastery, when he asked the most important question of all: "…what is inherited and how?"[21]

Enter the physicians

Napp was able to ask his question not only because of the patient work of the breeders and the focused intellectual life in Brno, but also because, by this time, it had become apparent that there was a force of heredity that could be studied[23]. As Carlos López-Beltrán has shown, that conviction, and the introduction of the term 'heredity' into the study of nature, came neither from scientists nor breeders, but from French physicians.

It had long been known that, like legal rights, some human diseases were 'hereditary'. For example, in the seventeenth-century, the philosopher Sir Francis Bacon wrote that: "Long Life, is like some Diseases, a Thing Hereditarie, within certaine Bounds."[24] However, as Bacon indicated, these characters were rarely consistently passed down from generation to generation ("within certaine Bounds"), and above all the lack of a noun ('heredity') to go with the adjective ('hereditary') shows that there was no realization that there was an underlying common cause of these phenomena[25].

The studies of polydactyly that were carried out by Maupertuis and Réaumur were part of the growing trend for eighteenth-century French physicians to study hereditary diseases (FIG. 4). The initial spur for much of this interest came from a competition that was organized by the Académie de Dijon in 1748, in which thinkers were asked to answer the question: "How are hereditary illnesses transmitted?"[26] Two further discussions were organized in 1788 and 1790, by the Académie Royale de Médicine, around the question of whether any illnesses at all were hereditary, in which physicians distinguished between diseases that were directly inherited and those in which only a predisposition was passed from generation to generation (FIG. 5).

As a result of this work, thinkers became convinced that there was a force that expressed itself across the generations, altering the characters of individuals. The reification of this conviction took form, not only as a growing field of study of pathological characters, but also in the identification of this force with a noun — 'heredité' — which became widespread from 1830 onwards. The English equivalent was first used in print by Spencer in 1863, and was used by Darwin in his notes around the same time[25]. Language had come into line with thinking, and scientists and physicians were now convinced that there were consistent — if bewildering — relations between parents and offspring.

Once heredity had been recognized, the challenge was to turn the conception of heredity as a force into what Jean Gayon has called "…an organizational or structural conception of heredity" — in other words, a conception in which heredity was based on particles[23]. Mendel's experiments on hybridization in peas led him to adopt a particulate understanding of heredity in which some 'recessive' particles were not expressed, but could reappear in later generations (his insight was made easier by his choice of traits with discrete classes; matters might have been different had he measured a continuous variable). Darwin's wide reading of the massive amount of data that were produced by breeders led him to also favour a particulate approach to heredity, in which some characters were 'invisible' or 'latent'. From this point on, the study of heredity began to move from a description of tendencies and forces to the search for the hereditary particles that produced characters, interacted and allowed evolution by natural selection — the units of heredity.

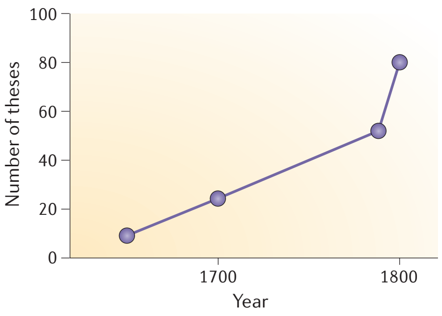

Figure 5 | **Number of French medical theses on hereditary illnesses, 1650–1800.** Data from REF. 11.

Conclusion

It took humanity a remarkably long time to discover that there are consistent relations between parent and offspring, and to develop ways of studying those relations. The raw phenomena of heredity were sufficiently complex to be impervious to 'common-sense' reasoning, to the brilliant but stifling schemas that were developed by the Greek philosophers, and even to the stunning forays of the early scientists. What was required was not a novel piece of apparatus, nor even a new theory; the key thing that was needed was statistically extraordinary data sets. On the one hand, these were composed of many reliable human pedigrees of unusual or pathological characters; on the other, they were the large-scale experimental studies that were carried out consciously by Mendel, or as a by-product of the commercial activity of eighteenth-century livestock breeders.

Like all great truths, heredity seems obvious once it is understood. But the fact that so many people took so long to realize what we take for granted does not mean that our predecessors were stupid. Instead, it indicates that, before the patterns within hereditary phenomena could be detected, society had to develop to a sufficient level for these kinds of data to be collected, examined, compared and intepreted. However, although science, written family records and large-scale agricultural production were the prerequisites for the discovery of heredity, the birth of our science was not simple, and required bold thinkers who were prepared to resolve an issue that had perplexed humanity for thousands of years. The result — the twin fields of genetics and evolution — represents one of the greatest insights in human history.

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