COMMENTARY

CLONING, INBREEDING, AND HISTORY

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THERE WAS much publicity after Wilmut and colleagues (1997), from the Roslin Institute in Scotland, successfully cloned a lamb from the udder cell of an adult sheep. The cloning of "Dolly" evoked great controversy, and even prompted a ban on further research in this field or, at least, in research on human cloning (Stewart 1997). The research focused on the integrity and continuity of the genome during the course of animal development, and the resulting achievement opened the way for new far-reaching inquiries on both cellular and molecular levels (Wilmut et al. 1997). The innovative technique of breeding sheep for meat production, which was developed by Robert Bakewell (1725–1795), presents a remarkable analogy, since it evoked a long-lasting spectre of consanguineous mating over 200 years ago (Orel 1998). Both achievements came from investigations on sheep in Great Britain. An examination of this analogy offers an interesting perspective on the acceptance of cloning by scientists and the public.

Greater attention should be paid to Bakewell's achievement, as well as its impact on the early study of heredity. His breeding method, known as *breeding in-and-in*, reduced the bone structure of sheep by half and doubled the weight of meat. This method depended on the skillful use of inbreeding within the selection process. Soon he was known among animal breeders for creating new, highly productive animal strains. But consanguineous mating was opposed on religious grounds by animal breeders on the Continent. Toward the end of the century, only Ferdinand Geisslern (1751–1824), in Moravia, was using inbreeding, and this was for the improvement of wool production in sheep. Shortly after 1800, he was acknowledged as the "Moravian" or "Austrian" Bakewell. The high breeding value of rams, from both Bakewells, soon increased their price up to fifty times, and occasionally even more (Orel and Wood 1981).

Even before 1800, professor F Fuss at the university in Prague rejected inbreeding in his book on agriculture because of the harmful effects of progeny degeneration (Fuss 1795). J Petersburg (1757–1839), manager of the new sheep breeding farm of the Archbishop of Olomouc, defended inbreeding in a versed inscription placed in 1796 above the entrance of the new farm; it indicated that healthy, noble sheep were produced there among the progeny of ewes paired with brothers, sons, and fathers (Nestler 1838). The inscription also

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appeared in a printed pamphlet, circulating among sheep breeders, which asked Fuss to provide proof of the harmful effect of inbreeding. Petersburg criticized the noted French naturalist G L Buffon (1707–1788) for his negative views regarding the crossing of animals from different environments as a general method of breeding in order to improve the animals, because he "inoculated his false ideas into the heads of unthinking farmers and it will be very difficult to make them free from the spectre of consanguineous mating" (Nestler 1838 in d'Elvert 1870:148–149). Similarly critized was the Cistercian monk from Würzburg, Ch Baumann (1785), who in his remarkable book on animal breeding recommended changing rams in the herd every three years to avoid the degeneration of the progeny.

The achievements of Geisslern inspired Ch C André (1763–1831), an outstanding naturalist and a leading thinker in economics and in the development of the sciences, to establish in 1814 the Sheep Breeders Society in Brno, in order to encourage the improvement of wool production. The breeders from central European countries attended the annual meetings and paid great attention to breeding methods, then treated as "scientific breeding." The exchange of ideas that arose from their observations and field experiments on selection, the application of inbreeding, and transmission of traits that determine wool quantity and quality, led the protagonists in 1819 to generalizations included in empirical *genetical laws* (Orel and Wood 1998). When considering the influence of inbreeding on hereditary defects, those of humans were also mentioned.

The participants repeatedly noted the achievements in animal breeding, which prompted T A Knight (1759–1867), who later became the president of the Horticultural Society of London, to apply artificial fertilization in creating new varieties of fruit trees (Orel 1978a). In 1816, André followed Knight by establishing the Pomological Society in Brno. He asked G C L Hempel, the secretary of the Pomological Society in Saxony, to explain the application of Knight's method for creating new cereal varieties. In an extensive essay, Hempel (1820) enthusiastically wrote about the great "triumph of higher scientific pomology," which opened the way for creating new varieties of all domesticated plants. But all this work depended on understanding the *law of hybridization*.

J K Nestler (1783–1841), a professor of natural history and agriculture at Moravian University in Olomouc, included in his teaching in 1827 the latest findings in scientific animal and plant breeding, which were treated in the same natural science framework (Orel 1978b). He wrote about the "generation with heredity" and defended the application of consanguineous mating, opposing views held by professors at the University of Vienna. Nestler published his lectures in Brno in 1829, and he evoked new discussion on the *theory of breeding*. These discussions about heredity reached a climax between 1836 to 1837; they separated heredity from the enigmatic term "generation," and presented heredity as the most important problem to be solved.

The more precise formulation of the problem, as the physiological research question, "what is inherited and how?", came from C F Napp (1792–1867); he was abbot of the Augustinian monastery at Brno that accepted Mendel into the monastery in 1843 (Orel 1975). Summarizing the discussion, Nestler (1837) wrote that breeders in Moravia soon "rejected the spectre of inbreeding," which was considered as a component of scientific breeding. He was aware that the difficult problem of heredity had already been tackled by many serious thinkers in the past. Acknowledging the 40-year tradition of sheep breeding in Moravia, he recommended an investigation of the transmission of parental traits to progeny as recorded in the available pedigree and traits records. From this approach, he expected an explanation of the enigma of *Vererbungsgeschichte* (hereditary history) or *Entwicklungsgeschichte* (developmental history), considered by Nestler as two aspects of the same phenomenon.

Some breeders were still afraid that close consanguineous mating might result in organic weakness or in chronic hereditary defects in the progeny. In order to help clarify the issues, Nestler (1839) published a paper entitled "On inbreeding," which explained that successful breeders do not use close consanguineous pairing alone. In this way Bakewell created famous new animal strains. Nestler concluded: "If parental forms did not possess undesirable traits the breeder can expect with great probability progeny without such defects. In the progeny of more closely related parents, defects can be seen in offspring with greater probability" (p 123). He added that there is no animal without any defect or, at least, without any potential (*Anlage*) for the defect. Between 1839 to 1841, Nestler and other champions of sheep breeding in Moravia died, and cheaper wool from Australia began to be imported to Europe. In this new climate, the Sheep Breeders Society in Brno ceased to exist.

The next step forward in the study of animal breeding came from Stuttgart, where, since 1821, Ch C André had been the leading advocate for the improvement of agriculture (Wilhelm 1867). His influence can be traced in the activity of an enthusiastic expert, A Weckherlin (1749–1868), manager of the king's estates and later director of the School of Agriculture at Hohenheim (Uhland 1988). In his masterpiece, *On Agricultural Production*, Weckherlin (1846) concluded that sheep breeding had great potential for discovering the principles of animal breeding, and gave great credit to the work of the Moravian Sheep Breeders Society. In his book, *Contribution to the Opinion on Constancy in Animal Production*, Weckherlin (1860) rejected the prevailing dogma of "constancy of race" and stressed "the victory of individuality over the race." Heredity, the special capacity that determines the transmission of parental traits to progeny, and treated as a force influenced by environment, was stressed as the basis of all breeding methods. Its explanation could depend on uncovering the degree of constancy of traits. Another influential expert in animal breeding was H Settegast; he came from the Weckherlin school of thought and the experience of sheep breeders in Moravia, and developed a new *theory of individual potency* (Settegast 1861, 1878).

Recently, J Gayon (1996), in his attempt to explain the origin of the scientific concept of heredity in the development of animal breeding in Germany, concluded that the treatment of heredity as a force, analogous to the forces in physics, became the main research obstacle up to the end of the century. This point of view was previously confirmed by another German expert in animal breeding, H E Nathusius (1872), who wrote: "The law of heredity is not yet recognized as the apple from the tree of knowledge, which has not yet fallen in the way, according to story, that brought Newton to his discovery of the law of gravitation" (p 120).

Following the achievements of Knight, plant breeders in Moravia, and in other countries as well, did not even try to explain the enigma of heredity. W Bateson (1899) had still doubted whether science had anything to contribute to horticultural breeding practice. Seven years later, on the occasion of the first Genetical Congress in London, he changed his view, stating that, thanks to Mendel, "the scientific and practical have gone to form a perfect and fertile hybrid" (Saunders 1907:60). He expected the complete union of both sources of knowledge to occur within the next hundred years. At that time he was not aware that the prescientific and practical hybrid had been developed nearly a hundred years earlier by sheep breeders, leading to scientific animal and plant breeding before Mendel was born.

From the analogy of the Dolly affair and the spectre of inbreeding, we can learn how unwilling the public can be to accept scientific (and even prescientific) discovery. The theoretical impact of the breeding in-and-in method had to undergo persistent objections by the public, as illustrated by Nestler (1839): "It seems to me remarkable that for the last fifty years the old conflict of inbreeding has been revived approximately once a decade" (p 125). The increased knowledge finally led to critical research on the problem of heredity. Its solution emerged as late as 1900 with the acceptance of Mendel's theory, which was derived from experiments in plant hybridization 35 years earlier.

The achievements of scientists from the Roslin Institute, which were the result of theoretical inquiries, opened the way for a deeper understanding of genome continuity during animal development. The researchers contributed to the study of animal cloning, a basic idea that was already known. Nuclear transplantation from somatic cells allows for the production of clones of domestic animals that have been selected for highly efficient genomes. "Closed races," arising from breeding in-and-in, were improved by geneticists in the 1930s as "inbred lines," and could be succeeded in the future by "cloned lines." The responses to these achievements by the public calls for a ban not only on human cloning but also on the research in this field. A similar case was the brief, initial moratorium that restricted recombinant-DNA research in 1976. Yet fundamental research cannot be hindered. Such theoretical achievements will also find applications in medical research.

An editorial in *Nature* points the way: "The history of technology suggests, however, that highly regulated human cloning will, after all, be found to be a tolerable way to proceed" (Editorial 1997:1).

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