

## A life of Dolly

### **Why was Dolly created?**

The development of the cloning technology was an extension of Roslin Institute's interest in the application of transgenic technology to farm animals. Transgenic mice have been available since the early 1980s. They are produced by a very sophisticated method of genetic modification through a technology using embryonic stem cells. Cells in culture can be genetically modified in very precise ways: removing genes, substituting one gene for another, introducing a single base pair change in the genetic code. In mice it was possible to genetically modify these cells, introduce them into a mouse embryo and the resulting mice that are born would be chimaeric (containing some normal cells and some genetically modified cells). At least some of the offspring of these chimeras would contain the very precise genetic modification. Since embryonic stem cells had not been isolated from farm animals, this method of genetic modification was not available. Cloning was therefore a potential alternative way of achieving the same end.

### **Birth**

Dolly started her life, as with all other cloned animals, in a test tube. Once normal development was confirmed at 6 days, the embryo that was eventually to become Dolly was transferred into a surrogate mother. Pregnancy was confirmed by an ultrasound scan at about 45 days of gestation and the pregnancy was monitored closely for the remaining 100 days. The pregnancy went without a problem and Dolly was born on the 5th July 1996. Unlike many cloned animals who often have neonatal problems at birth, Dolly was a normal vigorous lamb and was standing and suckling unaided within minutes. The animal technicians were aware that this was an important lamb and critical to the research team that had produced her but they were completely unaware of the impact she would finally have.

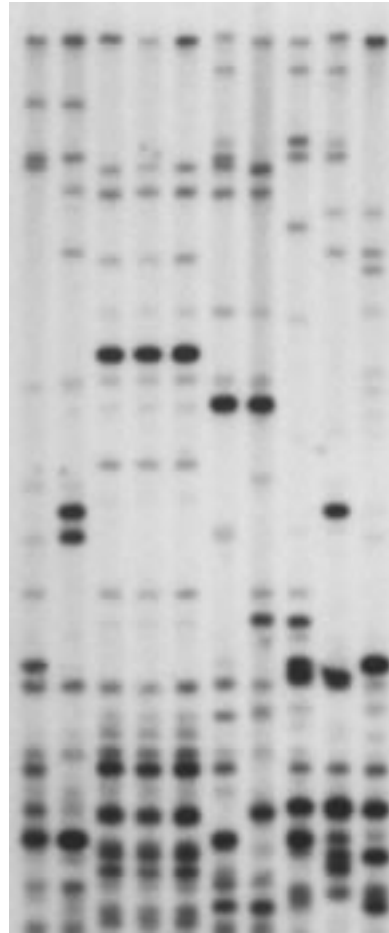


### **Announcement to the world**

The birth of Dolly was kept under wraps until the publication of the results could be prepared. Once these results were released, the full impact of the discovery became plain to all the animal carers as the world's press descended on Roslin. Most staff thought that this initial interest would be brief and quickly fade, but that was not the case and the press, in all shapes and forms, regularly visited Dolly for one reason or other for the rest of her life with interest peaking every time there was any concern over her health or when another species was cloned.

### Was Dolly already 'old' at birth?

The first wave of increased press coverage occurred when, at one year old, tests revealed that Dolly's telomeres were shorter than those expected for sheep of that age. Telomeres are sections of DNA found at the end of each chromosome. When the chromosomes are replicated during cell division a small portion of the telomeres are lost. They get shorter and shorter as more cell divisions occur and as animals age. This led to speculation in the press that animals cloned from cells obtained from an adult animal would age prematurely and die early. This was later shown to be untrue and in fact the telomere length is restored during the cloning process. Although Dolly's telomeres appeared shorter than other sheep of a similar age they certainly were not of an old animal. Extensive health screens carried out at the time failed to identify any abnormality with Dolly that would suggest premature aging.



### Dolly's family

In an attempt to allow Dolly to have as normal a life as possible and to demonstrate that she was physiologically normal it was decided that she should be allowed to breed. A small Welsh mountain ram was selected as her mate and between them they successfully produced 6 lambs. Their first, Bonny, was born in the spring of 1998. Twins followed the next year and triplets the year after that.



### Dolly's arthritis

Press interest in Dolly had quietened down for a while until, in the autumn of 2001 and at the height of the Foot and Mouth outbreak in the UK, Dolly was seen to be walking stiffly. An x-ray was essential, and after getting permission from DEFRA for a special movement licence, Dolly was transported to the Royal (Dick) School of Veterinary Studies (R(D)SVS). Here a general anaesthetic was administered and thorough investigations of her lameness carried out. The x-rays confirmed that Dolly did indeed have arthritis. This was a blow to everyone and again fuelled the suspicion that cloned animals were destined to age prematurely. The cause of the arthritis was never established but daily anti-inflammatory treatment resolved the clinical signs within a few months.

### **Dolly's final illness**

Although the arthritis was a concern for the animal carers at Roslin, a much more serious problem was feared. In January 2000, another cloned sheep, Cedric, died. The post mortem revealed that Cedric had died of sheep pulmonary adenomatosis (SPA). This disease is caused by a virus that induces tumours to grow in the lungs of affected animals. The virus is infectious and spreads from sheep to sheep by close contact. The disease is incurable.

The animal carers were clearly concerned that Dolly might be infected with the same virus but hoped that she could still be free of infection as Cedric had been housed in a separate pen to Dolly. She was immediately placed in isolation; she could see and hear other sheep and was housed with her first lamb Bonny but was prevented from mixing with all other sheep. Even worse news soon followed when in March, Morag, one of the first cloned sheep from cultured cells, succumbed to the same disease. She had been housed with Dolly for many years so the chance that Dolly was not infected were slim. When, in September one of Dolly's second litter of lambs was also diagnosed with SPA, it became certain that Dolly herself must be infected. At that point it was decided that her isolation served no purpose and Dolly was returned to the flock of cloned sheep.

SPA was a difficult disease to cope with; there were no blood tests available to confirm the diagnosis and no effective vaccines or treatments. The most important task was to ensure that, if Dolly did develop the disease, she should not be allowed to suffer. In addition to her regular daily health checks by the animal care staff, veterinary examinations were increased and her weight was measured weekly. Dolly was as far as could be established perfectly well. She remained healthy until Monday the 10th February 2003 when an animal care worker reported that he had noted Dolly coughing. Full veterinary examinations and blood tests were conducted but failed to establish a diagnosis. Further investigations were necessary and with the kind co-operation of the Scottish College of Agriculture and the R(D)SVS a CT (computer tomography) scan was carried out on Friday the 14th February 2003. The scan confirmed our worst fears, tumours were growing in Dolly's lung. Since a general anaesthetic had been necessary to perform the CT scan it was decided that it would be best if Dolly did not regain consciousness and an overdose of an anaesthetic agent was administered to end her life.

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