Embryos, cells, genes – and Society

If one believes, as I do, that the task of science is not merely to understand the world, but to change it for the better, it is fortunate that determinism plays little part in biology, that the environment exerts such a profound influence on development, at all levels – the external environment, the maternal environment, the tissue environment, the intracellular environment. My own research has always been on mice, as the most appropriate animal model for our own species; it has never been directly applied, but there has always been some human relevance in mind. And I have always felt it important to tell people in general what I am doing and why, what other scientists are doing, and what are the implications (both good and bad) of scientific advances.

For twenty-two years I worked for the British Agricultural Research Council. First in London, Dr. Donald Michie and I kept mice at hot, cold and intermediate temperatures, and found that the temperature of rearing influenced not only external features (size, tail length, ear size) but also their variability. Then we used the previously pioneered technique of embryo transfer to analyse a maternal effect on number of lumbar vertebrae in crosses between two strains of mice. Was it the origin of the egg that was important, or the uterus in which the embryos developed? It turned out to be the uterus, and this remains one of the few good examples of the uterine environment influencing an anatomical character. Frustratingly it was impossible at that time to pursue the finding further: it would be thirty years before techniques for examining the molecular basis for gene expression during development came on line. With Dr. John Biggers, I used the same embryo transfer method to show that early embryos removed from the female and cultured for 24 hours in the laboratory would develop into normal fertile mice. That result was to have important consequences, which perhaps explains in part why I am here today.

Moving to Professor Waddington's Institute in Edinburgh, I worked for some years on implantation, seen at that time as a promising target for contraception. Although I made certain advances, I was again frustrated by the elusive nature of the crucial local signal for implantation that the embryo gives to the uterus, a signal that has still not been identified. At about the same time, Tarkowski invented his embryo-aggregation technique for making chimeras, and I realised that chimeras provided the ideal situation for examining the effect of a tissue environment of one genetic type on a cell of a different genetic type. With this in mind, I looked at various aspects of development, in particular hair colour and sexual differentiation. Today, of course, studies of cell-cell signalling can be conducted at the molecular level.

After Edinburgh, I worked for 18 years for the Medical Research Council, as Director of the newly constituted Mammalian Development Unit. Up to that time, the developmental biology of mammals had been a somewhat neglected and under-funded topic in Britain, at least from the medical point of view. Studies on sex determination with a number of wonderful colleagues led me to a consideration of the factors influencing the sex of germ cells, the all-important cells that eventually give rise to sperm and eggs. Throughout their lengthy and fascinating developmental history, germ cells have turned out to be closely dependent on their tissue environment. The unfertilised egg, the final product of female germ cell development, itself provides a unique cytoplasmic

environment, which can reprogramme a specialized cell nucleus to support development of a new cloned embryo.

If germ cells are removed from their normal environment and cultured in the presence of certain chemical factors in the laboratory, they change into stem cells, which will survive and proliferate indefinitely. These stem cells are pluripotent, meaning that they can give rise to any of the cell types in the adult body. We and others are concerned to find out how pluripotent stem cells can be induced to form pure populations of specialized cells, which in the human could be used to repair damaged or diseased tissues – for example, nerve cells for Parkinson's disease, heart muscle cells for heart disease, insulin-producing pancreatic cells for diabetes. With germ-cell-derived stem cells, it will be important to ensure that the marks imposed on the DNA of certain so-called imprinted genes during germ cell development do not cause any abnormalities in the specialized tissues to which the stem cells give rise. During the next ten to twenty years, stem cells derived from adults, from foetuses, or from early embryos, may well revolutionize the treatment of degenerative diseases. The ethical and social implications of this field are under active discussion in many countries. Japanese centres are in the forefront of the scientific advances and are also involved in this ethical debate.