A germ layer is a group of cells in an embryo that interact with each other as the embryo develops and contribute to the formation of all organs and tissues. All animals, except perhaps sponges, form two or three germ layers. The germ layers develop early in embryonic life, through the process of gastrulation. During gastrulation, a hollow cluster of cells called a blastula reorganizes into two primary germ layers: an inner layer, called endoderm, and an outer layer, called ectoderm. Diploblastic organisms have only the two primary germ layers; these organisms characteristically have multiple symmetrical body axes (radial symmetry), as is true of jellyfish, sea anemones, and the rest of the phylum Cnidaria. All other animals are triploblastic, as endoderm and ectoderm interact to produce a third germ layer, called mesoderm. Together, the three germ layers will give rise to every organ in the body, from skin and hair to the digestive tract.

Gastrulation differs across species, but the general process is the same: the hollow ball of cells that forms the blastula differentiates into layers. The first phase of gastrulation produces a two-layered organism comprised of ectoderm and endoderm. The ectoderm will form the outer components of the body, such as skin, hair, and mammary glands, as well as part of the nervous system. Following gastrulation, a section of the ectoderm folds inward, creating a groove that closes and forms an isolated tube down the dorsal midsection of the embryo. This process of neurulation forms the neural tube, which gives rise to the central nervous system. During neurulation, ectoderm also forms a type of tissue called the neural crest, which helps to form structures of the face and brain. The endoderm produced during gastrulation will form the lining of the digestive tract, as well as that of the lungs and thyroid. For animals with three germ layers, after the endoderm and ectoderm have formed, interactions between the two germ layers induce the development of mesoderm. The mesoderm forms skeletal muscle, bone, connective tissue, the heart, and the urogenital system. Due to the evolution of the mesoderm, triploblastic animals develop visceral organs such as stomachs and intestines, rather than retaining the open digestive cavity characteristic of diploblastic animals.

Christian Pander, a doctoral student of Ignaz Döllinger at the University of Würzburg, in Würzburg, Germany, first recognized the existence of germ layers in chicks (Gallus gallus) in 1817. In the publications derived from his dissertation, Pander described how two layers of cells, which he called serous and mucous, gave rise to an intermediate layer, which he called vascular. Pander wrote of the interdependence of these three layers as well as the necessity of their interaction to form organs.

In 1825, eight years after Pander’s initial descriptions, Martin Rathke, a physician and embryologist from Prussia (now Poland), discovered layers of cells in a developing invertebrate crayfish, Astacus astacus, that corresponded to those Pander had described in chicks. Rathke showed that the embryonic layers Pander described existed in animals outside of the vertebrate clade. Karl Ernst von Baer, a professor of anatomy at the

Discussion of the germ layers dwelled over the next twenty one years, but they resurfaced when Thomas Henry Huxley, a natural historian in England, published "On the Anatomy and Affinities of the Family of the Medusae." In that 1849 text, Huxley suggested that adult jellyfish (Medusae) possessed two tissue layers, which he called foundation membranes, that relate to each other in the same manner that Pander had observed of the serous and mucous layers in the chick embryo. Huxley realized that a correlation existed between the body architecture of the adult jellyfish and the vertebrate embryo. Based on that association, Huxley attempted to integrate the study of vertebrates with that of invertebrates, and to unite studies of development, or ontogeny, with studies of organismal relationships, or phylogeny. The relationship between ontogeny and phylogeny, later called recapitulation, would be adopted and expanded by proponents of evolution, including Charles Darwin, in England, and Ernst Haeckel, a professor of comparative anatomy at the University of Jena, in Jena, Germany.

In the six years following Huxley's publication on Medusae, embryologist Robert Remak, in Germany, refined germ layer theory in two ways in his treatise *Untersuchungen über die Bildung und Entwicklung der Wirbelthiere* (Studies on the Formation and Development of Vertebrates). First, while working as a microscopist, Remak noticed that all of the germ layer cells of the chick embryo derived from the original single cell of the fertilized egg. Thus, Remak concluded, all cells originate from division of pre-existing cells, a conclusion that became central to cell theory. Second, Remak provided histological evidence for the existence of three distinct germ layers and traced the derivatives of each throughout chick development. Few noticed Remak's contributions to cell theory and research on germ layers.

In 1867 Aleksandr Kovalevsky, professor of embryology at the University of St. Petersburg, in St. Petersburg, Russia, published a series of studies that showed the presence of germ layers among invertebrates. Kovalevsky's work established the universality and homologous nature of the germ layers within the animal kingdom.

According to Jane Oppenheimer, a biologist and historian of science who worked at Bryn Mawr College in Philadelphia, Pennsylvania during the twentieth century, Kovalevsky's research prompted some of the most prominent scientists of the nineteenth century to research on the germ layers. The concept of the germ layers as invariant across species soon became entrenched and formed the basis of germ layer theory. Germ layer theory held that each of the germ layers, regardless of species, gave rise to a fixed set of organs. In 1872 Ernst Haeckel combined observations of germ layers with evolutionary theory to hypothesize that an unknown two-layered organism, which he called a gastraea, was ancestral to all other animals; this came to be known as the Gastraea Theory. One year later, Edwin Ray Lankester, Professor of Zoology at University College, London, in London, England, published a theory similar to Haeckel's along with a classification of all animals based on their composition of germ layers: homoblastic, diploblastic, and triploblastic. Researchers still use Lankester's classification.

In the late 1870s, several years after Haeckel's and Lankester's publications, many embryologists challenged germ layer theory and Haeckel's Gastraea theory. Wilhelm His, Rudolf Albert von Kölliker, and Oscar and Richard Hertwig, all in Germany at the time,
objected to the germ layer theory. In a series of publications from 1878 through 1881, the Hertwig brothers provided evidence that the germ layers had greater capacities for differentiation than most scientists recognized. In 1881 the Hertwigs formulated their Coelom theory, which focused on the role of mesoderm and also introduced the term and concept of mesenchyme, a type of animal tissue derived mostly from mesoderm.

Amid the varied arguments supporting or denying germ layer theory, some embryologists in the 1890s began to refocus their efforts on methods that could help them further understand how animals develop, and they employed physical manipulations of embryos rather than purely observational or descriptive embryology. In 1901 Charles Sedgwick Minot, a professor at Harvard Medical School in Boston, Massachusetts, predicted that the transplantation of cells from one germ layer onto another resulted in those cells adopting the fate of their new environment.

More than twenty years later, in 1924, Hilde Proescholdt Mangold and her doctoral advisor at the Zoological Institute in Freiburg, Germany, Hans Spemann, found evidence for Minot’s prediction and dismantled the foundation of the germ layer theory. Mangold harvested presumptive ectoderm from the dorsal lip, a tissue that organizes the gastrula stage, of an embryonic newt and transplanted this tissue to a different germ layer of the gastrula of a second species of newt. The transplanted ectoderm responded to the local environment on the developing host newt, and induced the formation of an extra head, nervous system structure, or extra body. That experiment demonstrated that the fates of germ layer cells are not entirely predetermined at the start of development.

In the fifteen years following Mangold’s work, embryologists continued to explore the potential for the three germ layers to differentiate along different routes and they produced evidence that further weakened the germ layer theory. Sven Hörstadius, professor at Uppsala University, in Uppsala, Sweden, used echinoderms, such as sea urchins, to study how germ layers differentiate. He employed transplantation, recombination, and fate mapping experiments to investigate the capacity of the germ layers to transform into tissues atypical of normal differentiation.

Throughout the remainder of the twentieth century, researchers continued to accumulate evidence that invalidated the theory that germ layers are pre-defined or highly-fated tissues. Following the works of Spemann, Mangold, and Hörstadius, scientists further explored germ layer potential for varied development. In the early 1950s Robert Briggs, at Indiana University in Bloomington, Indiana, and Thomas King, at the Institute for Cancer Research in Philadelphia, Pennsylvania, transplanted nuclei from the presumptive endoderm of the northern leopard frog, Rana pipiens, into eggs from which they had removed the nuclei. Briggs and King tracked the development of these transplanted nuclei to explore the timing of cell differentiation, and with those experiments they laid the foundation for future research in cloning. In the late 1960s Pieter D. Nieuwkoop, at the Hubrecht Laboratory in the Royal Netherlands Academy of Arts and Science, in Utrecht, Holland, discovered that endoderm induces adjacent ectoderm to form mesoderm. In the 1980s scientists shifted their focus towards identifying the genes that induce structural differentiation of the germ layers. Researchers in the early twenty-first century investigated the regulatory networks through which individual genes interact to cause germ layer differentiation.
Sources

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