Preface

In 1924 an article appeared in a German scientific journal describing the most important experiment in all the history of Embryology and probably one of the most influential pieces of research in the whole field of Biology. The first author of this paper, Hans Spemann, was Professor of Zoology and *Rektor* of the University of Freiburg at that time. The co-author, the results of whose doctoral thesis provided the basis for this paper, was Hilde Pröscholdt, a young doctor from Gotha, Thuringia, a central region of Germany. In accordance with the tradition of the times, she recently had her family name changed to that of her husband, Otto Mangold, who was the preferred disciple of H. Spemann. Sadly, Hilde Mangold died tragically on the year in which this article was published. Some years later, Hans Spemann, in his well-known 1938 book "*Embryonic Development and Induction*", entitled the chapter in which he describes the results of this work as "*The Experiment of Hilde Mangold*", thus leaving a noteworthy testimony to his affection for Hilde and his correct recognition of her merit. We thus choose the title "**Spemann-Mangold Organizer**" for this special issue of "*The International Journal of Developmental Biology*", in the hope that this term will eventually substitute the more usual denomination of "Spemann Organizer". In this way, we wish to honor the memory of Hilde Mangold and contribute to the just recognition of her contribution to the discovery of the organizer.

As is well-known, the aforementioned article by H. Spemann and H. Mangold laid the foundations of the phenomenon of embryonic induction and tissue differentiation, by first reporting the process of "primary" embryonic induction, which started with the appearance of the organizer at the beginning of gastrulation. Today, after many years of difficult research, embryonic induction is beginning to be understood as a complex and sequential chain of cellular interactions involving chemical signaling and differential gene expression. In fact, we now know that an earlier primary induction begins even before the appearance of the Spemann-Mangold organizer. Many future discoveries, not only regarding embryological development, but also the biological interpretation of cancer, will depend on the continuing of research on the subject of embryonic induction.

In the interests of brevity, we can classify the progress made since the now remote date of 1924 into four relevant overlapping periods. During an initial phase of observation and confirmation of the phenomenon of embryonic induction in different species, the classical, experimental embryological techniques of microsurgery and histology were used. Subsequently, during the thirties, a frustrating period of searching for the elusive inductive substances followed, in which the relatively crude biochemical techniques of that time were futilely employed to isolate biochemical components which we now know today are present in only minute quantities. This frustration made many researchers abandon the quest for the mechanisms underlying embryonic induction, with only very few research groups insisting on the subject from the fifties to the seventies of the last century. These minor groups were headed by such people as Sulo Toivonen, Osamu Nakamura, Heinz Tiedemann, Pieter Niewkoop and Conrad Waddington. Indeed, this journal has dedicated monographic studies to these prestigious scientists in the past: 1989 (Vol. 33 Nº 1), 1994 (Vol. 38 Nº 2), 1996 (Vol. 40 Nº 1), 1999 (Vol. 43 Nº 7) and 2000 (Vol. 44 Nº 1) respectively.

However, during the last two decades of the 20th Century, a fresh impulse was given to this type of research by the complementation of the classical techniques, with the newer experimental approaches including modern cell labeling methods, immunological techniques and in particular, molecular biology and developmental genetics. As a consequence, the advances over the past few years have been astonishing. New molecules and regulatory principles have been identified and it has become possible to isolate genes characteristically expressed by the Spemann-Mangold organizer and to study their properties. A number of genes specifically expressed in this region of the organizer, were shown to function as transcription factors, controlling the expression of other genes. These transcription factors include the homeobox genes *Goosecoid*, *Lim-1, Xnot, Otx2, Siamois, Xanf-1* and *HNF3-beta*. The function of these genes is to control the expression of secreted factors that in turn participate in the patterning of the embryo. These secreted proteins include Noggin, Follistatin, Chordin, Frzb-1, ADMP, Dkk, Nodal-related, Cerberus and others. One of the unexpected results has been that many of these molecules which participate in embryo patterning are themselves inhibitors of well-known growth factors, such as those encoded by Bone Morphogenetic Protein (BMP), Wnt and Nodal-related genes.

Studies in various species have contributed to our improved knowledge of the functioning of the organizer. Much fruitful work has been conducted in *Xenopus* following classical approaches using urodeles. Mutagenesis screening in the zebrafish has led to the identification of mutations in organizer-specific genes such as *Xnot* (floating head) and *chordin* (chordino). In the mouse, the homologues of most of the aforementioned genes have been inactivated by targeted gene mutation. In chick embryo grafting experiments, implantation of beads loaded with growth factors has led to a renaissance of the study of avian gastrulation. These molecules act in the extracellular space and their activity can be regulated by proteolysis. Undoubtedly, some of the novel secreted factors will prove to be useful to induce cell differentiation *in vitro* and may even find applications in tissue replacement therapy.

Using these approaches in different species, some aspects of organizer function seem now to be well understood. For example, the recent genetic screening in zebrafish shows that BMP signals act on the late gastrula to promote ventral development of the three germ layers. Studies in *Xenopus* have demonstrated that one of the earliest signals is beta-catenin, which promotes dorsal development already at early cleavage stages. During the intervening period spanning from early cleavage to late gastrula, a plethora of molecules comes into play and their exact functional inter-relationships are at present being unraveled. Mouse knockouts revealed the singular and redundant function of the various implicated genes, suggesting that we are only at the beginning of the dissection of the complexities of embryonic patterning.

The contents of this monographic issue are a good indication of the present flourishing of new groups all over the world, who dedicate their efforts to achieving a better understanding of what has incorrectly been termed, even nowadays, "primary induction". Encouraged by this enthusiasm, we recently celebrated in Madrid during 24-26 May 1999, an international workshop under the auspices of the Spanish Juan March Institute. This workshop was entitled *"Molecular Nature of the Gastrula Organizing Center: 75 years after Spemann and Mangold"* (see the meeting report by A. Nieto in *Cell*, Vol. 98, pp. 417-425, 1999), deliberately reminiscent of the title of the famous book *"Organizer. A Milestone of a Half-Century from Spemann"* by Osamu Nakamura and Sulo Toivonen. The objective of our workshop was to revise the enormous progress which had been made in this area in the previous twenty five years. Many of the participants at this meeting in Madrid have contributed to the production of this special issue of *"The International Journal of Developmental Biology"*. Others were subsequently invited to complete the celebration of this magnificent discovery by H. Spemann and H. Mangold, by fundamentally describing the historical framework and the theoretical implications of this work. We feel that these articles have inestimably contributed to the enrichment of this publication.

We would like to finish this introduction recalling a statement by Benjamin Lewin, the well-known and prestigious editor of the journal *Cell,* who chaired one of the Madrid meeting sessions. Referring to the 1924 H. Spemann and H. Mangold article (the English translation of which is reproduced in this issue; see pp. 13-38), which was the fundamental basis for the concession of the Nobel Prize to Hans Spemann in 1935, he claimed that such an article, with its structure, content and type of experimental description, would probably not be considered acceptable for publication by any journal editor nowadays, even if the phenomenon of embryonic induction had not yet been discovered! Such an apparent incongruity gives us an idea of the enormous technical progress which has been made in modern experimental embryology and of the demanding standards of scientific journals in recent years. However, the intellectual contribution represented by the 1924 paper, has been largely unrivalled since then, despite such rapid technical progress. Nevertheless, the articles which comprise this issue are a valuable example of both technical and intellectual progress. It is our hope that this special issue will prove to be a stimulus to further contributions in the future.

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