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The organizer concept and modern embryology: Anglo-American perspectives

TIM J. HORDER*

Department of Human Anatomy and Genetics, University of Oxford, U.K.

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The discovery of the organizer by Hans Spemann (1869-1941) and Hilde Mangold (1898-1924), over seventy five years ago, must surely be ranked as one of the single, most momentous episodes in the modern era of developmental biology. And yet, when one recalls that there have been periods when it was all-but-forgotten (as I will explain below), it is clear that the history of the subject is far from straightforward. This paper deals with the confusing story of the impact, fate and consequences of the discovery, primarily in the UK, but briefly also in the USA[19]. It so happens that British embryologists exerted important influences in determining the direction of developmental biology following the discovery. Julian Huxley (1887-1975)[20], probably the best known British embryologist at the time, along with Gavin De Beer, played a significant early role in alerting English language readers to Spemann's finding. Joseph Needham (1900-1995)[21] and Conrad Waddington (1905-1977)[22] in Cambridge were significant figures in steering the research strategy that emerged in the 1930s following on from Spemann's work, through attempts to identify the chemical nature of the organizer.

Present-day readers can perhaps sense the excitement generated by the discovery through the words of one particularly insightful eye-witness; *"Experimental embryology attained a commanding position in the field of Biology during the first half of this century. To biology students of my generation, it held the same fascination as molecular biology and neurobiology do today..... the Spemann-Mangold organizer experiment of 1924..... was widely regarded as the crowning achievement of this period"* (Hamburger, 1988, p. vii). In its day the impact was certainly worthy of comparison with that of the discovery of the DNA double helix in a more recent era. Ample evidence will emerge as the account unfolds in this paper.

But over the last thirty years another concept has dominated developmental biology as powerfully as the organizer did before the war, namely the concept of "positional information" (PI). This was very much the single-handed construction of Lewis Wolpert[23]

Notes:
Frequently quoted sources are referenced in abbreviated form in the text as follows: EDI ("Embryonic Development and Induction", Spemann, 1938); H (Hamburger 1988); HH (Holtfreter and Hamburger, 1955); HW (Horder and Weindling, 1986); S (Smith, 2000); SM (Spemann and Mangold, 1924).These references may be found at the beginning of the References section of this paper

A Glossary (Notes 1-18) may be found at the end of this paper, defining the main embryological terms used herein.

***Address correspondence to:** Tim J. Horder. Department of Human Anatomy and Genetics, University of Oxford, South Parks Road, Oxford OX1 3QX, U.K. FAX: +44-1865-272-420. e-mail: tim.horder@human-anatomy.oxford.ac.uk

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in London and it introduced an entirely new term to the literature. The role in the theoretical superstructure of embryology once occupied by the organizer is now occupied by PI; both seek to identify the mechanisms thought to explain the essence of embryogenesis, namely what controls the orderly laying out of anatomical structures during development. This, at least, is the contention that I want to document in this paper and my overall objective is to show how this conceptual sea-change might have come about. These two concepts would probably not be compared or even connected by most developmental biologists today, but it is the aim of this paper to show that there are strong historical links between them and that an understanding of these links illuminates much about the field of developmental biology.

Hamburger has provided a uniquely felicitous description and interpretation of key events in the evolution of work on the organizer. In summing up his overall view, he has this to say; *"While the efforts of the experimental embryologists to subject animal development to causal analysis were remarkably successful, they have left a legacy of unfinished agenda which can be left unattended to for a few decades but should not fall into oblivion"* (Hamburger, 1988, p. viii). His concluding discussion (p. 171-2) hints, by subtle and polite implication, that Hamburger is puzzled by the relation between the organizer concept (particularly in its application to the more general developmental mechanism of induction) and Wolpert's notion of positional information. In my judgement the two concepts are fundamentally at odds with one another and in this paper I want to throw light on the reasons for such a deeply unsatisfactory situation.

The approach and aims of this paper

This paper is, in equal measure, both a scientific and a historical contribution. Addressed to both scientists and historians, it is a study of conceptual issues basic to our current understanding of embryology while also being a study of how that understanding has been arrived at. This dual aspect - I see no tension here; in fact I see science and history as inseparable - is crucial. This study is intended as a demonstration of the importance and value of considering scientific problems in a historical framework.

The underlying incompatibility between PI, the approach that has prevailed, and the classical approach to embryology embodied in the organizer, together with the closely connected concept of induction, has interested me for some time. As part of a review of the general subject of embryonic pattern formation shortly after Wolpert introduced his model (Horder, 1976; to be summarized later), I argued that there was a perfectly tenable (and preferable) alternative to PI based on a broadened understanding of the concepts of induction pioneered by Spemann. In a nutshell, I will argue here that the steps that have led up to the success of PI can, and indeed must, be "explained" largely in terms of historical forces. Wolpert can be seen as one step in a historical chain reaction of which Spemann was a major part. Part of the explanation for what amounts in the PI model to a dismissal of embryonic induction lies in the cumulative effects of developments occurring during the 45 year interval separating the two concepts. In so far as Wolpert stands as a key representative and theorist of our present era, it is clearly of some significance if concepts and evidence derived from Spemann happen, for historical rather than scientific reasons, to have been excluded by recent theoretical trends.

These two conceptual developments epitomize the subject of embryology before and after the Second World War. My analysis of the issues arising in connection with the origins, meaning and consequences of these concepts within developmental biology, encapsulate, to a remarkable extent, the development of the field over the entire twentieth century. Hence my concentration on them alone: I am dealing only with one line of investigation within the subject of embryology. (I am, for example, not dealing with descriptive or medical embryology, or evolutionary and comparative aspects). Rather than cover the details of the discovery of the organizer itself (already discussed in Horder and Weindling, 1986) I will be focusing on what it has represented in the context of the central defining issues of embryology as a whole. A long time scale needs to be considered in this account because, as I hope to convince the reader, the inertia in the evolution and later use of fundamental concepts is very great and therefore we are dependent today on a long heritage of assumptions and beliefs in ways we do not often recognize. The patterns of thought that Spemann learned around 1900 may (though perhaps in themselves now strictly irrelevant) have detectable repercussions in Wolpert's views. Readers impatient with the perspectives of 1900 are recommended to jump ahead to page 102.

It is important that I explain and justify the "methods" I am adopting in this paper. I have always assumed that to mix science with history is a hazardous enterprise, particularly because it is so easy to twist and exploit history in order to offer support for a scientific position. I remain in no doubt that, indeed, such an exercise offers many snares and delusions, especially when dealing with currently relevant scientific issues in which one is oneself involved as an embryologist. On the other hand, it is my belief and experience that considering the origins and significance of the history behind a scientific issue, which is not explicable "logically" or fully accounted for in its own, purely scientific terms, is often the key to understanding and "making sense" of it. Furthermore, it is when current aspects of science are considered in this way that such aids to understanding are potentially of most interest and value for scientists today.

One overriding requirement of historical method has dictated the structure of this paper. A proper understanding of the history requires that one avoids the cardinal sin of "Whiggism" or "presentism" (i.e. judging the past by today's standards or in the light of knowledge unavailable at the time). I have tried hard throughout the paper to respect the obvious truth that past events can only validly be understood according to the perspectives appropriate to the time concerned. Scrupulous attention to sequences in time is important too because much of the "explanation" of historical episodes arises directly out of the actual timing and sequence of events. However there is an important rider to these essential truths, based on the distinction one can draw between the original events themselves and our ability to know about and "understand" them subsequently. In any historical exercise it is necessarily the case that the historian's view of the past has to be *expressed* in contemporary terms (thus, for ease of understanding I will sometimes use modern words in describing episodes which are obscure as originally expressed), but an additional factor also applies. Paradoxically, present understanding of past events can sometimes be more complete than understanding at the time, and the historian can potentially define earlier thinking more clearly than was actually then achieved. That this can be true is a reflection of the increasingly balanced view that comes with "distance", the result of increased awareness of more facts, circumstances and context. Factors, which may be powerful causes of events, can often go unspoken, unrecorded and even unnoticed at the time. *"Most scientists tend to concentrate in their publications on new fact or rather on new discoveries..... At the same time they usually fail to record important ongoing changes of concepts or emphasis"* (Mayr, 1982, p. 18). "Unconscious" factors are many (Bevir, 1999); any scientific argument relies on multiple layers of hidden assumptions. The balanced, distanced view of the historian looking back needs time to consolidate; it does not necessarily entail Whiggism since this can be actively avoided, but it does require energetic (and often elaborate) efforts to make allowances for present perspectives and to reconstruct one's own mode of thinking towards modes of the past.

In the case of scientific thought we have a somewhat special situation in which the distinction between the two forms of reality (the reality of immediate, present experience, and the broader reality of retrospective understanding) is perhaps easier to accept. Ways of thinking and argument in science are, relative to other areas of human experience, unchanging at least over recent generations. Science is also distinctive in having rational and definable aims (and to a large extent, a rational methodology) which operate consistently over time, despite changes in techniques. Moreover scientific understanding is strictly a cumulative process, which operates by adding new layers onto the superstructure steadily built up over the past, and in this sense operates very much as a historical process - present events are subservient to, and only of interest in so far as they connect with and add to, the process. These features of science offer support to the claim that it is both feasible and valid to infer and reconstruct aspects of thought that were not recognized consciously, let alone recorded, in the past. By inference from actual events and from passing phrases (and by "putting oneself in their place" by means of the relative transferability of the "scientific frame of mind"), it is possible to reconstruct the aims, and the conceptualizations of problems, that were actually less than clear to participants in a past era. Pickstone (1995) discusses some of these interesting issues of historical method further.

In order to avoid Whiggism and bring out the importance of the sequence of events and the cumulative nature of the scientific process, my account is chronological (although divided up into broad periods only) and I have therefore left my own scientific viewpoint and final historical interpretation until the closing section (Section 2; 2.1-2.3). The main sections in the paper give accounts of the scientific perspectives as they developed in each historical phase, with an emphasis on how scientists perceived problems and solutions at the time rather than laboratory events. To avoid bias, I rely heavily on quotations from the participants themselves. Where possible I also refer to accounts by other historians, but in general, embryology has not been extensively studied historically (compared for example to genetics and evolution). Because my aim is restricted to the analysis of only broad brush conceptual shifts - in fact it concerns only two major theoretical positions - the evidence I adduce, even though only very selectively sampled, is hopefully adequate. The volume of supporting evidence potentially available is massive. After each main section, I append "commentary" sections, as an additional step in attempting to separate hard historical evidence from interpretation. Without going beyond evidence and concepts available in the relevant period, I want in these sections to point out the choices, misunderstandings and uncertainties implicit and emerging at the time, though often not overtly expressed. This, of course, is the very essence of scientific "advance"; at every point success or failure depends on decisions and judgements regarding selection from among the choices of scientific direction constantly on offer - choices which involve priorities, aims, assumptions (unwarrented or justified), spotting new possibilities, assessing practicalities, etc.

In short, I aim to consider the historical and the scientific issues on an equal footing. This is a balancing act that, though impossible to "get right", is worth attempting. If science and history are to inform each other, and I am strongly convinced that they can and must, then their point of greatest intersection will lie with important *current* (rather than antiquarian) scientific issues; there historical considerations will be most relevant, interesting and useful to scientists today. In my view history impacts on scientists in many and significant ways (Horder, 1998). I will return to this general theme briefly at the end of the paper.

SECTION 1

1.1 The discovery of the organizer in its context

In Hamburger's words *"Spemann and H. Mangold's experiment consisted of the transplantation of the upper lip.... (of the blastopore of the gastrula stage of the early salamander embryo).... from one embryo, the donor, to the flank of another embryo, the host. In order to be able to distinguish between donor and host tissues in microscopic preparations, the unpigmented embryos of one species were chosen as donors and the pigmented embryos of another species as the hosts. To the surprise of the experimenters, three days after the operation, a nearly complete secondary embryo had formed on the flank of the primary (host) embryo....The remarkable feat of the upper lip of the blastopore, a small piece of tissue, in producing an integrated whole embryo has earned it the designation of organizer"* (H, p. 6-7; reference citations given in this abbreviated form refer to selected, key sources, see p. 97) (Fig. 1)

Our main objective is to examine and understand the impact of this discovery. To do so we need to start by reconstructing the interpretation that was put on the discovery at the time. This is the aim of the present section; I will cover the lead up to, and initial interpretation of the finding in the period up to 1925. Huxley and De Beer were most influential in the UK in this period; they would later centre their substantial and influential textbook of 1934 on Spemann's discovery. The succeeding section deals with the years 1925-1940, which culminated in a focusing on the chemistry of the organizer that was to influence perspectives for some time to come. In this period Needham and Waddington became leading contributors.

To understand what Spemann meant by the "organizer"[14] it is necessary to take fully into account the perspectives, priorities, options and assumptions that Spemann brought to it as a result of his scientific training starting around 1890. As we shall see, his background explains much about how he arrived at the discovery and also his way of interpreting and presenting it. I can only touch on the main trends among the many background factors, and on the best known of the many biologists whose work had a formative

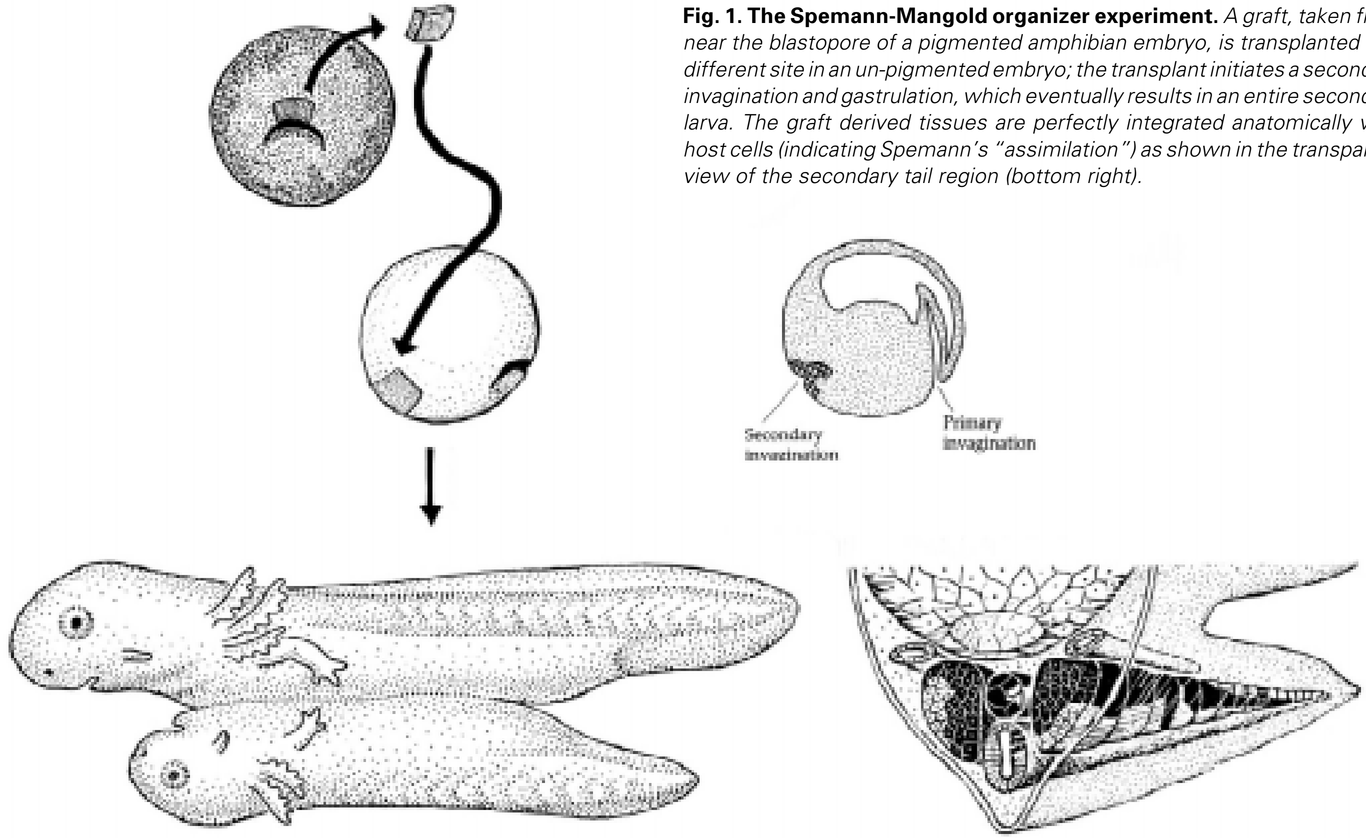

Fig. 1. The Spemann-Mangold organizer experiment. *A graft, taken from near the blastopore of a pigmented amphibian embryo, is transplanted to a different site in an un-pigmented embryo; the transplant initiates a secondary invagination and gastrulation, which eventually results in an entire secondary larva. The graft derived tissues are perfectly integrated anatomically with host cells (indicating Spemann's "assimilation") as shown in the transparent view of the secondary tail region (bottom right).*

impact on Spemann's line of reasoning. In attempting to cast one's mind back so far, one has to remember in particular that over the period 1890-1920 general biological knowledge (and understanding) was indeed "primitive" by our standards. So many basic facts were unknown (especially about the microscopic and submicroscopic levels, i.e. concerning the nature and status of cells and large molecules) that what now seem to us totally unwarrented ideas - even sometimes disprovable by facts known at the time - were quite standard. If it seems difficult for us now to believe that biologists accepted literally some of the notions addressed below, it is worth recalling that biology was still at a stage in its evolution when vitalism was a perfectly respectable and even common belief, i.e. it was a real possibility that living organisms represented a completely different form and realm of existence, constitution and functioning from that known to the rest of science in the physico-chemical world (see Neal,1916).

Important perspectives, issues and assumptions in the period prior to the discovery of the organizer

(a) *How could hereditary factors be separated out from developmental factors? Embryology overlapped heredity and neither domain was in practice easily separable.*

The usual, logical account of the history of genetics gives the impression that the clarification of chromosome behaviour in gametogenesis and fertilization during the 1880s (linked to the idea of a "germ plasm" passed between generations and also to the disproof of Lamarckism - the inheritance of acquired characters - in which Weismann was particularly influential), prepared the ground so that, with the rediscovery of Mendel's laws in 1900, the basis of genetics (the linking up of material units on chromosomes and patterns of inheritance) fell rapidly into place. By 1920 Morgan's elucidation of *Drosophila* genetics was virtually complete. But this picture misrepresents what biologists actually understood at the time.

The fact is that the subjects of embryology and heredity were inseparable in most people's minds. This was in part the result of the experimental material used; understanding of chromosome behaviour in reproduction (and as a possible basis for the germ line carried across generations) was worked out, by such supreme exemplars as Boveri and Wilson, using eggs and early embryo material, for the simple reason of their large cell size. As Spemann began his research career, Boveri was his esteemed teacher and mentor (Baltzer, 1967, HW). Over the period of Spemann's direct association with him, 1894-1908, Boveri created key concepts equally relevant to embryology and genetics, as they would later separately emerge. The founders of American genetics, Wilson and Morgan[24], were both trained as embryologists and would probably always have regarded themselves as such.

At the time there were fundamental uncertainties as to whether genetic factors could (via variation) form the basis of Darwinian natural selection. These were fueled by the debate (Bateson and de Vries versus Pearson) which revolved around the factorial (saltationist) versus biometrical (statistical, gradualist) views of genetic action. The uncertainties were such that at the turn of the century Darwinism was very much in doubt and Lamarckism was making a strong come back (see Nordenskiöld, 1928; Bowler, 1992). Many of the leading protagonists and opinion-formers of the period at one time accepted a role for a form of Lamarckism, including Brooks, O. Hertwig, Driesch, Pauly, Wolff, Conklin, Child and J. Loeb. Spemann certainly shared such views (Fässler, 1997, p. 303-8). Bateson remained sceptical about the chromosomal basis of genetics until 1920. One important step had however been taken. By 1883 it had been accepted that the nucleus was the seat of hereditary factors (which were often termed "idioplasm"). Weismann, Roux, Boveri and many others had begun to unravel how nuclear factors might become differentially expressed in the egg cytoplasm and embryo cells.

The separation of the provinces of genetics and embryology was a long, slow and sometimes painful business, and certainly more complicated than recognized by the standard histories of genetics. For the average biologist the separation only really began to become clear in the 1930s: the "Modern Evolutionary Synthesis" (the restatement of Darwinism based on population genetics), as finally consolidated in the 1940s, can indeed be seen as the first full clarification of the place of the discipline of genetics within biology generally. Given the uncertainties around the turn of the century, it is understandable that there remained much confusion regarding such matters as the distinctions between the respective roles of nucleus and cytoplasm or between considerations autonomous to the organism and those dependent on interactions with the external world. Given possible Lamarckian mechanisms, adaptation and selection could be plausibly accounted for by factors in the environment directly imprinting their effects on the organism or cell (or cytoplasm or nucleus). The concepts of "memory" and inheritance were often used to throw light on each other (hence notions such as "ancestral reminiscence" or the influential ideas of Bergson, Semon, Hering or Butler) (Russell, 1916, 1930; Nordenskiöld, 1928). The apparent indications of direct Lamarckian environmental interactions with the mechanisms of inheritance must have seemed much more potent and immediate than the abstract, scattered and controversial Mendelian evidence derived from breeding studies and pedigrees.

Spemann has sometimes, probably unfairly[25], been accused of ignoring genetics. By the time of Spemann's main work the domains of genetics and embryology were beginning to be separable in methodological terms, but conceptual demarcation was still unclear. If one attempts to reconstruct a picture of how the average biologist thought about "heredity" at this time, he would have thought of the basic layout of body parts as being inherited directly by organ localisation ("promorphology") in the egg cytoplasm (inherited maternally through the ovary or imposed in some way by environmental stimuli) while leaving the fine tuning of details to "genetic factors". "(T)he cytoplasm of the egg is the future embryo (in the rough) and ....the Mendelian factors only impress the individual (and variety) characters upon this rough block" (Loeb, 1916, p. 8). Even in 1931 it could be said (as written almost certainly by Huxley) that

> *"the first rough laying out of the future body is apparently not due to the genes: it is due to the protoplasm of the egg...... A large and tangled subject, the Physiology of Development! Soon, we hope, it will straighten out, and the interplay of gene and protoplasm, of organizing zone and encumbering yolk, of mechanical stress and internal secretion, will be better understood" (Wells et al., 1931, p. 326).*

(b) *In what descriptive and explanatory terms could the morphological patterning of organisms be understood?*

The prominent phenomenon of the partitioning of the egg during its cellular cleavage was one of the earliest subjects of embryological study, out of which many issues emerged in often confusing ways; how did cleavage relate to partitioning of nuclear idioplasm; how did cleavage planes relate to future embryonic axes; how predictable were cleavage patterns; what forces controlled them? Pflüger and Roux started relevant explorations around 1882.

One version of this approach became known as "lineage tracing". This tradition[26] (which was pursued "especially by American embryologists" (EDI, p. 10); it could be called the Whitman school, of which Wilson was a part (Baxter, 1976; Maienschein, 1978, 1986, 1987)) was based on the tracing of the development of visible, intrinsic pigmentation patterns in the egg and early embryo or on tracking the succession of daughter cells. This approach gave accurate, reproducible descriptions of the unfolding of embryonic development provided cell mitotic patterns were consistent (as in cases of "determinate" cleavage). Favourite organisms were transparent and preferably rapidly differentiating. Such considerations meant that marine invertebrates were particularly popular and these were readily accessible in congenial surroundings at the new marine biological stations. The implication behind all this work (which was purely descriptive, and no different in principle from what would later be called "fate mapping"[7]) was that organization was present from the start of development. The term "promorphology" (a Haeckelian term) describes exactly that position. This work harked back to attempts to trace ancestry and homology in the earliest stages of embryogenesis - the nineteenth century "evolutionary morphology" tradition - and recalled the implications of Haeckelian "recapitulation" (Gould, 1977). On the other hand many embryologists (including Boveri and Spemann) sought to distance themselves from Haeckel (as leading exponent of the discredited recapitulationary approach). It is worth remembering that almost all the leading biologists of the time started their scientific lives performing studies in the lineage tracing mode; including Weismann, Bateson, Conklin, Lillie, Brooks, Wilson, Morgan and Spemann. They therefore started from a position according to which they tacitly assumed an element of "preformed" organization in the egg cytoplasm. As genetics became better defined, embryologists (such as Conklin, Lillie) were driven in reaction to see a sharp opposition between promorphology, based on the egg cytoplasm, and genetic factors located in the nucleus. The implications were ultimately anti-genetic, since emphasis was placed by embryologists on the cytoplasm.

If we try to single out what biologists in the period 1890-1920 might have regarded as their ultimate, primary objective, their focus was on "the origins of form". The objective of "explaining" morphology, form or "organization" (they were virtually synonymous) was the most insistent problem that presented itself to biologists simply because this was the aspect of living organisms that was most obvious to all. There is no doubt that it was this problem that had dominated biology throughout the entire nineteenth century (Horder, 1998). Moreover, by the end of the century, when in descriptive terms the complexity of embryos and adults was now well and accurately known, the science of evolutionary morphology (including comparative embryology) was highly developed. Dominance of the issue of form and its origin no doubt explains a number of linkages between areas of interest that now strike us as far from straightforward. Thus regeneration (Churchill, 1991) was equated with embryogenesis; single cell organisms were thought of in terms indistinguishable from those applied to the most complex multicellular forms (both were living organisms and possessed "individuality" and "integrity", even "personality"); cells as such were seen almost as an irrelevance (Whitman, 1893) given the priority attached to the organism as a whole; structure, organization, development and regeneration of plants and animals were compared interchangeably and on equal terms; egg stages were seen as possessing essentially the same properties as adults. (Powerful support for views of these kinds came, for example, from Lillie's demonstration of partial differentiation of the *Chaetopterus* egg into a larva in the absence of cell division (Lillie, 1902)). According to all such viewpoints, the whole came causally prior to the composing units, be they cells, organs, nuclei, molecules or hereditary determinants. Similar views were still being strongly reiterated by Child or by Russell in 1930 and Bertalanffy in 1933. At the start of the twentieth century there was no way that biologists could suspect the real complexity of cells, biological molecules or the genome. The modern concept of "cell differentiation" was one of the very last aspects of cells to be clarified, only gradually emerging in the 1920s (Maienschein, 1991)

Given such perspectives, one can see that biologists could freely jump between different experimental systems and species depending simply on availability and convenience; virtually any living system could be used interchangeably to investigate "the origins of form". Regeneration was seen to have a natural counterpoint in involution (or reorganization of tissues in culture) and both phenomena were loosely linked to the general matter of size variation under the catch-all term "growth". Regeneration offered significant pragmatic advantages over the study of embryos; the experimental organisms were potentially more accessible, larger, and not season- or location-dependent. For the young Spemann the recently discovered Wolffian regeneration of the lens bore potent lessons (still prominent in his discussion in his book of 1938; EDI, p. 78-82, 313-317); it showed the persistence of integrated (and adaptively advantageous) organizing morphological principles (as required to explain embryogenesis) operating even in adult organisms.

But in what terms was morphological organization understood? Organization was viewed in terms of such concepts as "axes", "axis formation", "symmetry" "polarity"[16] and laterality (as revealed by its reversal in congenital abnormalities such as *situs inversus*). Embryologists were particularly struck by such phenomena as twinning, "heterosis" (see Herbst, 1901), duplication of parts and mirror-imaging of such duplicates (i.e. "polarity" reversals). Many of Spemann's earlier papers approach and analyze organization (bilaterality, axis formation) in these terms. Such phenomena clearly held a fascination *per se.* The implication that deep rules of embryology (and genetics) might be revealed through such phenomena is implicit in the early studies of Bateson (1894), Pzribram, Child and Morgan. Roux's study of concrescence (Sander, 1991) shows how teratology was used as influential evidence; it yielded crude ideas on fate maps, bilaterality and axis formation. Spemann was still actively discussing such issues in 1919.

It was to take a considerable time before the questionable significance of lineage tracing (and the parallel concept of fate mapping) as indicators of causality in development, or the role of the egg cytoplasm, would became clear. These approaches to the embryo are essentially only descriptive and it required experimental interventions to disclose the underlying causal factors.

(c)*How could the causes of patterning be isolated and identified? Early use of the physiological approach showed how profound questions could be raised, and potentially answered, through an experimental method*.

The nucleus was firmly identified as the locus of the "germ plasm" (or "idioplasm") by 1883. This advance led on to the question of how the nucleus exerted its differential control on the dividing, separate cells of the embryo. How were the "determinants" contained in the nucleus apportioned? Weismann's "germinal selection" model assumed this process was automatic: but Boveri provided prominent evidence that the cytoplasm controlled it (Churchill, 1968). (Boveri (1887) obtained evidence for the notion of gene elimination through "chromosome diminution", a potential basis for determinant selection; he showed that it was cytoplasm-dependent (see EDI, p. 319)). The evidence from regeneration strongly implied that nuclear division is not differential (but rather that multipotency of determinants is retained throughout life in each cell that can regenerate a whole new anatomical organization). Multipotency of embryo nuclei was proved by (among other techniques) delaying or displacing nuclear entry into cleaving cells. Throughout Spemann's early work on early cleavage stages in amphibians this was a recurrent theme and it is still discussed in his 1938 book. Boveri, Hertwig, Pflüger and Driesch all ended up arguing the case that the cytoplasm controlled and mediated the influence of the nuclear "idioplasm".

If patterning of the embryo was mediated by the egg cytoplasm, how was this achieved? By way of testing Weismann's uncompromising theories Roux (1888) killed one blastomere in the two-cell frog embryo: the result was the development of a half-embryo as predicted on the Weismannian theory of "mosaic development"[13]. This ushered in the era of "*Entwicklungsmechanik*". This movement promoting an experimental approach (in part in reaction against the descriptive "evolutionary morphology" and the Haeckelian tradition) was commonly known by Roux's term, "*Entwicklungsmechanik*". Others preferred other terms; *Entwicklungsphysiologie* (Spemann), causal embryology (Brachet), experimental embryology, experimental morphology, or physiological morphology (His).

The movement was largely modelled on physiology. Physiology implied reductionism, chemistry and physics, and the isolation of simple, here and now (rather than evolutionary) causes. At first the search for causes took the form of identifying "stimuli", analogous to those triggering tropisms in lower organisms and plants. Child, Jenkinson and Loeb (Pauly, 1987) were leading examples of embryologists pursuing this search, with the underlying target of extreme materialism. Julian Huxley was soon to follow along a closely similar path. Loeb, whose mission was to show the simplicity of the links between living phenomena and physics, created a sensation when in 1900 he showed that simple osmotic shocking of an unfertilized egg could trigger the onset of development. A review listing all then known examples of "formative stimuli" (the forerunners of "induction") affecting development by Herbst in 1901 distinguished between stimuli internal and external to the organism (Oppenheimer, 1991). (Spemann used the word "correlation" to cover such internal causal interactions, as in his similar review, Spemann, 1907, see (HW Note 22)) "(The) investigative means ...to a clear-cut "question in mind" in the "environmental" circumstances in which the organism found itself... proffered an unmistakable invitation to the experimentalist. By controlled manipulation of environmental conditions; mechanical disturbance of egg or embryo, variation in light, temperature, pressure, chemical reagents or orientation in the gravitational or an electromagnetic field - the experimental embryologist began to produce artificially and then to codify the manifold responses of the developing organism. Such experimental work, best understood in its more mature form after 1900, began with a rush towards 1890. Embryology was entering a new and again exceptionally active phase" (Coleman, 1971, p. 55).

The power of experimental intervention (over and against mere blunt description) started to have an impact with Driesch[27], when he showed what he soon called "regulation"[18] in the sea-urchin embryo (in contrast to Roux's finding of "mosaic development", one part of the embryo, physically separated from the rest, developed into a *whole* larva)[26]. To describe the property that allows the embryo fragment to regulate Driesch also introduced the concept of "harmonious equipotential system"; this concept encapsulates the future central problem for embryology - how do embryonic systems achieve organized (and regulating) patterning from a starting point when all their component parts are (as shown by regulation) equivalently uncommitted and open to multiple possible developmental paths? Driesch directed attention to the issue of "determination"[3]; by defining a clear distinction between what a cell normally is fated to form ("prospective value") and its earlier potentiality to develop into a wide variety of cell types ("prospective potency"), he pinpointed the question of what causes the required selection from the range of potencies. For Driesch this set off a train of abstract, logical speculations which led him increasingly to dismiss not just preformation in the egg but any "machine theory" (of which Weismann was the extreme exponent) and to his notoriously abandoning of any hope of a strictly causal analysis. Finally his only solution (in his appeal to the philosophical principle of "entelechy") was an unabashed vitalism (Churchill, 1969). It was increasingly clear, however, that an interventionist, experimental and analytical approach could indeed reveal causes and separate out issues, such as the respective roles of nucleus and cytoplasm, or of genetic and epigenetic considerations.

(d) *What explanatory concepts were available to cover the phenomenology of early embryogenesis? Early theoretical concepts in Britain and the United States.*

The simple, almost crude, experimental techniques initially available meant that crude results emerged; and these in turn soon turned into crudely bi-polarized explanatory positions typified, not inaccurately, by the starkly opposed stances of Roux and Driesch. Further complicating notions such as "postgeneration" or "reserve idioplasm"[28] had soon to be introduced in order to accommodate evident inconsistencies in the evidence. At a time when no clear distinction between genotype and phenotype was made (or possible), the whole problem area tended to be expressed in terms of the long-standing preformation-epigenesis distinction (paralleled in Roux's distinction between "direct" and "indirect" development), now made more explicit, through the experimental approach, in the form of mosaic as opposed to regulative development. The experimental proof of promorphology became "mosaic development": but like Weismannian arguments based on genetic factors the implications were preformative, i.e. both these positions shared the problem that on their own they ultimately "explained" nothing about development (they imply an infinite explanatory regress to an earlier pattern of causes at the start of development, which itself then requires its own causal explanation). Regulation, on the other hand, requires some form of "epigenetic"[5] interpretation or in Roux's terminology "dependent determination"[28]. But the concept of epigenesis was in itself in a less than satisfactory position, due to its vagueness and its encouragement of arbitrarily invented explanatory mechanisms.

However a middle way between the bi-polar positions slowly emerged. Collectively a picture was being defined along the following lines; the pre-conditions necessary to explain the emerging morphology of the organism were built into the cytoplasm of the egg; a simple initial promorphology (or "germinal localization") was imposed on, or acquired by, the egg maternally or from external forces, e.g. gravity, light, point of sperm entry or oxygen supply from the ovary. The important realization was that the developing pattern of the embryo could later emerge gradually and multiplicatively through internal cause and effect (Maienschein, 1986). How could the internally established patterning be imagined in material terms? The available conceptual "models" were few, and based on analogy. Embryo organization was recurrently compared to crystals (Haraway, 1976), magnets (Driesch), fibres, "colloids". The analogies provided by behaviour and psychology were equally common: Spemann was much attracted in this direction, due to the influence of his friend Pauly, who promoted a brand of Psycho-Lamarckism.

Again Boveri was a pioneer in pointing the way forward. He is often credited with introducing the idea of an axial-gradient[9]; i.e., a graded or stratified differentiation in the egg cytoplasm which could control nuclear "germinal selection" and ultimately differentiation of parts in the embryo. "The gradient hypothesis....has proved not unfruitful in the experimental morphology of echinoderms. But if it had T. Boveri for its father, C.M. Child has been its prophet" (Needham, 1942, p. 496). Charles Manning Child[29] was entirely typical of this period. He argued that organisms were controlled by "metabolic gradients", a theory that was based on indirect evidence (i.e. differential susceptibility to poisons, rates of "activity" (meaning growth and mitosis) and differential staining by dyes). He invoked such concepts as "physiological correlation", regulation, dominance, privileged region, and polarity. Although applied to embryos, most of his work was based on evidence from regeneration, primarily in a variety of invertebrates. Child frequently drew parallels between development and behaviour (e.g. Child, 1924) - he wrote extensively in similar terms on the nervous system - suggesting a shared property of purposefulness or goal directness. He promoted his views widely from 1902 to 1946 in lengthy texts (e.g. Child, 1941) and in the journal he edited ("Physiological Zoology"). "(T)he studies by Child ....exerted the strongest immediate influence in transforming embryology into a physiological science" (Willier and Oppenheimer, 1964, p. 129). "(T)hough not always clear what he meant, Child's lengthy books show that he recognized aspects of the physiological complexity of development that many of his contemporaries either missed or did not wish to acknowledge" (Maienschein, 1997, p. 225).

Julian Huxley is interesting because he was probably the first in the Anglo-Saxon world to indicate the importance of Spemann's discovery and to discuss its implications, followed closely by his student Gavin de Beer. Moreover he was himself already a strong follower of Child's point of view; understandably given his similar early research interests studying regeneration, growth and involution, primarily in invertebrates. As Huxley would later say; "It is the great merit of C.M. Child to have shown in theory....(how the determination of the future embryo can arise out of a non-diversified egg)... is possible" (Huxley and De Beer, 1934, p. 7).

My intention now is to take the discovery of the organizer in 1924 as a starting point for my discussion of the meaning of the concept and its implications. I will only give the minimum of description of the steps, events or technical considerations that led up to the discovery (available in Horder and Weindling; 1986, Hamburger, 1988 and Fässler,1997). It was Spemann who, above all, showed the way in which the *Entwicklungsmechanik* programme could be made effective as an analytic tool. The objective of Spemann's earliest work was to confirm, and if possible refine, the analysis of the embryo which Weismann, Roux, Driesch and Boveri had begun. Until about 1900 (when Born and Harrison introduced grafting of embryo tissue) the available techniques were limited (apart from the variation of external conditions) to subdivision of the embryo (either by shaking or killing blastomeres by pricking). Throughout his career Spemann was admired for his technical skill (e.g. microsurgery and the invention of new surgical techniques) but equally for his almost dogged determination and persistence in refining unambiguous experimental designs capable of yielding clear-cut biological answers. The discovery of the organizer was a wonderful example of these characteristics; it uniquely brought together the appropriate combinations of techniques, clarity of design, clear conceptualization, and a decisive result that offered an apparently comprehensive "answer", which pointed towards mechanisms providing an epigenetic solution to the problem of development.

Spemann's first experiments used a hair loop to constrict the early amphibian embryo as a way of fully or partially creating double, regulative embryos, so demonstrating a Drieschian "harmonious equipotential system", but out of this also came early ideas on the possible controlling influence of one half of the gastrula (dorsal) on the ability of the other to differentiate. (H, p. 14). In his discovery of lens induction (1899-12) he established, for the first time, the criteria by which a chain of cause and effect can be proved within an embryo; it was possible to prove that the eye cup was both necessary *and* sufficient to cause the formation of the lens by transplanting the eye and/or the responding ectoderm that forms the lens into new combinations (either by transplanting the eye to positions elsewhere in the body or by causing foreign ectoderm to cover it). Looking back on this early work, in the light of the complexities that eventually came to cloud this initially straightforward discovery, Spemann would still insist that; *"this much seems to be certain; that in several if not all species of the* Amphibia *....the optic cup possesses the ability to activate ..lens formation"* (EDI p. 76)

Fig. 2. Hans Spemann (left) with Ross Harrison.

In order to facilitate my analysis of the conceptual route which Spemann took in formulating the idea of the organizer I first summarise the main events and the principal concepts that Spemann introduced (see Horder and Weindling (1986) and Hamburger (1988) for details):

1896; observes progressive wave of differentiation (termed "growth by addition" in 1903) in formation of ear.

1897; with aim of testing Weismann's theory and re-examining regulation, began work on amphibian egg and early embryo; constriction (with hair) leads to full and partial twinning.

1899; begins work on the lens; ablates eye cup and shows (through the resulting failure of lens development) what would become the classic example of "dependent determination"; the first example of "induction" in the modern sense. Suggests further techniques and tests (performed by Lewis in 1904). Conflicting results in different species led to continuation of this work until 1912.

1900; constriction experiments show that regulation only occurs in animal halves of divided embryos; notion of "differentiation substance" present dorsally and on which the ventral half is dependent.

1901; Boveri notes stratification patterns in cytoplasm of sea-urchin egg and introduces the concept of a "privileged region" as controlling force in development (EDI, p. 142).

1903; notes possibility of neural induction by underlying mesendoderm (EDI, p. 159); invokes a concept similar to Boveri's privileged region in the frog (SM, p. 182); concludes that determination is established only at the time of gastrulation.

1905-7; rotates segments of neural plate in neurula to examine regulatory and polarity adjustment.

1906; Braus describes "double assurance"; reviewed by Spemann in 1907.

1910; Boveri describes the cytoplasmic gradient concept, now in *Ascaris* egg.

1912; final review of lens problem.

1915; return to problem of determination at early gastrula stages. Aims to study the timing and location of stages of determination by exchange of tissue between different embryo regions; also by mutually rotating half embryos.

1916; uses *homeoplastic* graft transplants (between embryos of the same species) marked by differing levels of pigmentation. Transplants grafts to map locations of determined and undetermined tissue. First organizer result, interpreted only as "self-differentiation". Results published in 1918 and 1919.

1917; repeats experiments but using *heteroplastic* graft exchanges (between different species differing in pigmentation) in order to improve marking of tissues. Results published 1919 and 1921.

1918; now describes self-differentiating region near blastopore as "differentiation centre" (EDI, p. 142)). Introduces term "appositional growth" in place of "growth by addition".

1919; "differentiation centre" renamed "organization centre".

1921; brief first report and naming of "organizer" phenomenon. The term "field" is introduced.

1924; Spemann and H. Mangold definitive paper on the organizer.

Having surveyed in outline the background events and scientific perspectives that provided the context for the final discovery, we are now in a position to consider in detail how Spemann and Mangold presented their findings in a definitive, and now classic, paper of 1924.

Commentary: Although the discovery of the organizer had been announced briefly in 1921, Spemann and Mangold finally presented their results in a detailed paper in 1924. Initial reactions to Spemann's results were, anyway by present-day standards, slow to emerge, but increasingly excited. Huxley was one of the first to refer to them in print. Huxley had begun correspondence with Spemann in 1923 and published a paper on the implications of the organizer in *Nature* in 1924, connecting it immediately with Child's gradients[30]. De Beer, having written a textbook already incorporating the organizer (De Beer, 1924), visited Spemann in Freiburg twice (probably in 1926-7). By 1926 he refers to Spemann's work as; "this astounding analysis" (De Beer, 1927, p. 149) and describes how; "There is .....something in the region of the dorsal lip which exerts an extraordinary influence on the neighbouring tissues" (De Beer, 1926, p. 75-6). By 1929 Waddington was following up the discovery in Cambridge; and had probably also visited Spemann. Later he spent six months in Otto Mangold's laboratory learning techniques alongside the exceptionally gifted experimentalist Johannes Holtfreter (both were members of the Spemann school). Needham spent three periods in Mangold's laboratory, starting in 1933.

In the USA, Harrison (1933, p. 316), Spemann's only peer as an experimental embryologist, commented of the organizer; "Its powers are extraordinary, and almost anything brought into its neighborhood is made in some mysterious way to cooperate in forming an embryo of a varying degree of completeness". Conklin spoke of Spemann as one "whose experimental analysis of the development of the amphibian egg is the admiration of the scientific world" (Conklin, 1929, p. 31). Similarly Harrison judged that "The most important advance in embryology of late years has been Spemann's .... discovery of the organizer center and organizer in the amphibian egg" (Harrison, 1933, p. 316). Morgan was more cautious; "It might appear, without further explanation, that the organizator has a mysterious influence on the neighboring parts" (Morgan, 1927, p. 239). Harrison remarked on the "the opening up of this new Yukon to which eager miners were now rushing to dig for gold around the blastopore" (Harrison, 1925, quoted by Twitty, 1966, p. 39).

The most striking feature of Spemann and Mangold's interpretation of the organizer result, as we examine the evidence within the 1924 paper, is that they simultaneously maintained two quite distinct positions regarding the nature and mode of operation of the organizer. In unraveling the significance of this crucial point we immediately face a terminological problem. Spemann[31] included both mechanisms within the term "organizer". He also uses the word "induction", seemingly as a synonym of the "organizer". However, he did not have terms to distinguish the two mechanisms themselves. (It is quite possible that this was no accident[32]). Given that it is essential for us to keep the two mechanisms clearly separate, I will from this point on use the words "induction" for the first and "field"[8] for the second, since the two aspects of Spemann's organizer mechanism correspond approximately to what would currently be understood by these terms. *(In my usage the term induction refers to initiation of a specific pattern of differentiation, in embryo cells still with potential for a variety of forms of differentiation, by immediately adjacent cells which are themselves already specified as to developmental fate).* The reader must bear in mind that when these words are used in any quotations from the earlier literature included later in this paper they often have quite different meanings.

Spemann's first mechanism is an induction. When the organizer tissue (taken from a region where gastrulation is occurring) is transplanted to the distant site in a host embryo where it will initiate the formation of a secondary embryo, the organizer graft sets up a new process of gastrulation. Spemann is describing a mechanism whereby mesendoderm (including archenteron), formed as a result of the secondary gastrulation process triggered by the organizer transplant, causes the determination and differentiation of neural plate from the now immediately overlying ectoderm of the host. "everything..... could be merely the consequence of ....(the) secondary gastrulation" (SM, p. 174). Induction operates *between* germ layers (i.e. it is "vertical", from mesendoderm to ectoderm). Spemann's second mechanism (which I am dubbing the field mechanism) involves an influence carried directly (as contrasted to the indirect process involved in gastrulation and induction) from the organizer *within* a germ layer (i.e. "cell-to-cell" or "planar"); this influence spreads out within the surrounding germ layer and itself has an action which brings about cell determination and differentiation. "(A)fter the termination of gastrulation the implant continues to exert determinative influences on its surroundings" (p. 174)... "(T)he possibility exists of a determining effect progressing from cell to cell, not only....during the period shortly after implantation.....but also during later developmental stages (p. 179). "(D)etermination proceeds from cell to cell in the embryo. Such an assumption suggests itself whenever differentiation, that is, the visible consequences of determination, does not start in all parts simultaneously but, beginning at one place, progresses thence in a definite direction" (p. 180). Comparing the two mechanisms he says; "The ectodermal component of the transplant could have self-differentiated into the strip of neural plate, and could have caused the differentiation of ectoderm anterior and lateral to it progressively to form neural tissue. Or the determination could have emanated from the subjacent parts of the endo-mesoderm and have influenced .....components of the overlying ectoderm in the same way" (p. 153).

In order fully to understand Spemann's dualistic position it is important to appreciate some of the initial assumptions he brought to the situation. For some time Spemann had recognised the possibility of neural induction by mesendoderm[33]. Although it had long been known in general terms that cells invaginated through the blastopore during gastrulation to make the gut cavity, knowledge was rudimentary. Spemann's understanding of gastrulation was limited - his picture is suggested by a quotation from 1903 (EDI, p. 159) - and almost certainly involved an error. One has to remember that the first studies capable of adequately documenting the fate map and cell movements occurring during gastrulation in amphibians had not yet been undertaken[34]. (Vogt's classic fate maps[7] were published between 1923 and 1929). A number of misleading accounts were current, particularly involving the notions of "concrescence" and "delamination" (Fässler, 1997, p. 180). These ideas implied that mesodermal structures such as notochord and somites originated by migration from lateral regions or directly from the surface rather than through the process of invagination during gastrulation. Spemann's uncertainties regarding the fate map are well described in Hamburger (H, p. 23-47), who seeks in some detail to examine their significance. His "misunderstanding ...had some serious consequences" (H, p. 33) (e.g. in delaying his eventual crucial experiment) (Fig. 3).

We have above all to be clear what Spemann's objectives were at the time. All his work between 1915 and 1919 was directed towards examining the timing of determination and more specifically the "differentiation gradient" that he had begun to envisage spreading across the embryo. The notion (traceable back to the early ideas of assimilation, privileged regions and dependence of ventral on dorsal gastrula halves) became refined by 1918 when he identified the region near the blastopore as a source of "progressive determination"; as a result of experimentally rotating half-embryos he had narrowed down the location of the region from which the differentiation gradient might proceed. Using new methods, he was simultaneously refining his ability to examine how "differentiation...does not start in all parts simultaneously but, beginning at one place, progresses thence in a definite direction" (SM, p. 180). From 1916 he used homeoplastic grafting to transplant small regions of the embryo to new sites in order to map out the "progressive determination" in detail. Using the criterion of "self-differentiation" of the graft in its foreign surroundings he could establish whether a given region of the donor embryo had already become determined. As he mapped grafts from different sites (using the blastopore effectively as a marker of position), some came from near the blastopore and some of them, when transplanted distantly, produced secondary embryonic axial systems (i.e. the organizer effect, though not yet recognized as such).

In reconstructing how he arrived at his final result we have one invaluable incidental piece of evidence. We know, from his own account, that a letter Spemann received from Hans Petersen (probably in late 1918) represented an important step in the sequence of events (EDI, p. 143; H, p. 46). The point that Petersen seems to have prompted in Spemann's mind - though the elements were already well known to him - was that, if one

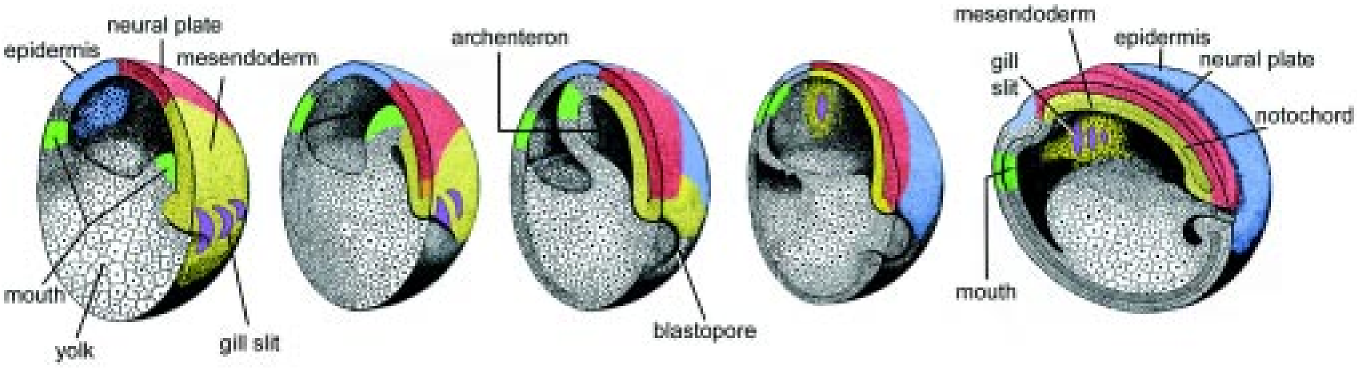

Fig. 3. The amphibian fate map. *Labelled, undifferentiated cells marked at the early gastrula stage (left) can be followed through their various morphogenetic cell movements during succeeding developmental stages until they reach approximately their final positions and begin differentiation at the neurula stage (right). A limited selection of tissues are shown colour-coded. Data based on the results of Vogt (1929).*

considers the blastopore region to be the mediator of gastrulation, then the transplanted blastopore could have been the source of invaginating mesendoderm, which (as a result of its migration) might have exerted a long-range influence on the host tissue, inducing neural tissue. If the inductive influence of the mesendoderm was involved in neural plate initiation, then the expectation would be that the neural plate in the secondary embryonic axis would be composed of *host* tissue. Although we do not know exactly what Petersen said, there seems little doubt that it was this spur which allowed Spemann's final experimental design to fall into place. Now it became crucial to establish how much the secondary axis was simply due to "self-differentiation" and how much host tissue was involved. Spemann had already (starting 1917) developed the demanding heteroplastic transplantation techniques which would allow him actually to detect which tissue was graft and which host. The effect of Petersen's letter was that it led him to realize that all he needed to do was to combine the two experimental protocols; i.e. to transplant a blastopore *heteroplastically*[35]. This is what Hilde Mangold, his student, successfully did for the first time in 1921.

The result once fully analyzed and published in 1924 showed that the graft had indeed caused the host tissue to be induced. Spemann concludes, in line with the argument raised by Petersen, that neural induction by the mesendoderm had been demonstrated, but where does the idea of the second mechanism come from? The answer surely lies in his much earlier ("cherished", H, p. 33)) concept of assimilation[36]; the second (field) mechanism amounts to just such a conception. A comment in the 1924 paper offers support for this interpretation regarding the continuity of his thinking; "If wishful thinking were permissable in questions of research, then we might hope in this case that the second of the previously discussed assumptions .....(i.e. the field mechanism).... would prove to be the correct one. For, if induction should be limited to a stimulus for gastrulation, then the problem of the harmonious equipotential system, which had just seemed to become accessible to experimental analysis, would right from the start confront us again in all its inaccessibility" (SM, p. 180). Here he is alluding to the situation before the discovery; the need to account for the Drieschian problem of explaining an integrated yet regulating pattern, as well as the progress he had already been making in tackling it. He evidently prefers the field concept. But he is also pointing out that the gastrulation-based inductive mechanism appears to contribute little towards a solution to this basic target. The continuity of his thinking is also implicit in the chain of changes in the terminology that he used. The idea of a "differentiation centre" dates from before Petersen's letter. This became the "organization centre" in 1919 and the "organizer" in 1921 with the new discovery[37]. Spemann's dualistic conception was not unanticipated (it was already part of how he thought about lens induction), nor did it require any unwelcome change to his thinking. The new element was that the discovery brought him nearer to identifying the forces mediating progressive determination. Spemann speaks of the "expected, and yet so surprising result" (EDI, p. 145). The comment seems exactly to capture what had happened.

If this interpretation is correct - and if, as seems certain, he already had available the necessary awareness of the concepts which came together in the experiment; about possible neural induction by mesendoderm, the role of the blastopore in mediating mesendodermal invagination and ideas about forces spreading directly along the surface, cell-to-cell, from a centre - then the question arises, why did he not think of the crucial experiment earlier and why was Petersen's letter needed as a trigger[35]? It seems likely that the possibility of, and need for, the final experiment had not occurred to him, simply because the experiments he was already engaged in depended on self-differentiation (any other, more complex phenomena would have been an irrelevant distraction) and were (in his own eyes) successfully leading to clues about mechanisms (in relation to which additional considerations such as the inductive mechanism would merely be an unnecessary complication). Petersen caused a number of pre-existing elements - methodological and interpretative - to be recombined simultaneously together.

Did Spemann's uncertainties about the fate map play a significant part in these developments? It is clear, as Hamburger points out, that Spemann was both vague, and inconsistent, on the issue of the location of origin of neural tissue in relation to the blastopore; strictly speaking his own evidence would have allowed him to arrive at the correct mapping. But these confusions could in no way have affected the nature of the explanations Spemann eventually arrived at; his earlier patterns of thinking are so close that their continuity cannot be in doubt. (Whatever misunderstandings he might have had about neural plate, his concept of fields operating within germ layers as demonstrated by assimilation of host and graft tissue was at least as striking in the mesoderm (SM, p. 174)). It is much harder to say whether his confusion might have delayed the discovery or prevented him in some way from seeing the need for the experiment which Petersen alerted him to. Given the inevitably slow pace of his experiments this would be hard to judge.

The coining of the term "organizer" had come about under somewhat unusual circumstances. It was first announced in a one-page appendix to the 1921 paper, added at a late stage. The term was introduced on the basis of a single experimental result; moreover, the one embryo showing the organizer result had not been fully analyzed since, we are told by Hamburger (H, p. 45) it was still alive at the time of writing. Thus only surface observations were possible; no histology as yet existed. There was an element of haste in the announcement of the "astounding fact" (EDI, p. 141). Spemann's introduction of a new word to describe his results is significant in itself. "Spemann's name for his discovery may at first sight seem rather grandiloquent, but is really quite reasonable and accurate" (Waddington, 1935, p. 69). Its inclusion in the title of the 1924 paper suggests that it was important to him[37]. Despite the continuity of the ideas, there was something new in the finding, and the 1924 paper makes it clear that he is using the new word to refer to the organizing "force" which he has come closer to identifying, and which supercedes the earlier notion of "determination stream". The distinction between "organization centre" and "organizer" signifies this; the former is reserved only for the physical location where the organizing factors reside. "The designation "organizer" (rather than perhaps, "determiner") is supposed to express the idea that the effect emanating from .. (the organization centre).. is not only determinative...(but has more complex patterning effects) (SM, p. 182-3). Spemann, nonetheless, points out that his analysis is only a first step (SM, p. 182). Although, typically, he is cautious about the relative contributions of the dual mechanisms, he was evidently predisposed to regard the field mechanism as the dominant one.

1.2 The organizer evolves towards the field concept; 1925-1940

In conceptual terms the period 1900-1920 had been, as Harrison (1937) remarks, a period of stagnation for embryology. Genetics was making the running in biology and embryology still confronted the most fundamental questions for which it had few substantiated answers. The discovery of lens induction some twenty years earlier, had been widely noted, but the subject had ground to a halt in confusion as anomalies and complexities emerged in the phenomenon. Lens induction did not seem a sufficient basis for a convincing, general epigenetic theory and had faded from interest. For these reasons alone Spemann's discovery of the organizer came as a new and fascinating development. Now an all-embracing approach to breaking through the Roux-Driesch impasse seemed possible, and experimentally amenable.

The discovery of the organizer had happened to come at a crucial time for biology. Development played a prominent part in a widespread discussion about the status of biology within science generally, and featured in a flurry of books in the area of "theoretical biology" [38], including Woodger's "Biological Principles" (1927), Driesch's "The Science and Philosophy of the Organism" (Second Edition, 1929), Needham's "The Sceptical Biologist" (1929), Russell's "The Interpretation of Development and Heredity" (1930) and Bertalanffy's "Modern Theories of Development" (1928/1933). The period of 1928-1930 seems to have represented something of a crisis point for many people; when Bertalanffy talks of the "crisis within biology", he has in mind the need to replace any vestiges of vitalism with a new form of rigourous and scientific concept, namely "organicism". According to Needham (1968) vitalism was still very much a realistic option for some scientists. Considerable insight into perspectives can be obtained from the activities of the "Theoretical Biology Club", based in Cambridge and London, which has been so well studied by Haraway (1976), Wersky (1978) and Abir-Am (1991). Under the influence of the new positivistic philosophy, an abiding concern was the defining of methods appropriate to biology and Woodger, an embryologist and philosopher at Middlesex Hospital Medical School (Roll-Hansen, 1984), here provided the driving expertise. Embryology was always close to the interests of this group. *"(T)he general tendencies of the newer developments in biology are reflected with special clearness in relation to the problem of development"* (Bertalanffy, 1933, p. 177). The theoretical biologists seemed to be modeling themselves on theoretical physics. This was a time when physics itself was in turmoil regarding fundamental assumptions and (through figures like Whitehead - famous for his "philosophy of organism" -, Eddington and Jeans) it seemed possible that physics could in turn learn new ways of thinking from the biologists. Both Needham and Waddington were members of this small circle of influential and forward-looking younger biologists.

It might seem that soon after the 1924 paper Spemann modified the emphasis of his interpretation in certain directions. His later (and final) position on the organizer effect is well summed up in his own words; *"While at the beginning....(the two mechanisms).... seemed to be of fairly equal value, the actual facts urge us more and more toward the exclusive adoption of the second one....(induction)".* However he adds that... *"The first possibility nevertheless has not yet been cogently excluded"* (EDI, p. 156). From 1924 a succession of new phenomena in amphibian embryogenesis were described, mainly by the Spemann school. A great deal of new and important evidence (often designed to test the mechanisms underlying the organizer effect, but some of it fortuitous) emerged in a short space of time. The evidence for Spemann's earlier theories became massively supported, and yet a careful reading of Spemann's publications after 1924 shows that he refined his ideas, particularly towards invoking the concept of fields. The new evidence, and the new concepts that accompanied them, cannot be reviewed here. Our main concern will be to trace the implications of Spemann's dualistic view of the organizer and how it might have been modified. We happen to have a unique opportunity to understand these complex (and often confusing) events through a remarkable document; Spemann's "Embryonic Development and Induction" (1936, translated into English in 1938), referenced as EDI throughout this paper. This is a difficult, comprehensive, multifaceted, but thoroughly logical, book which surveys all his work[39]. One complication in unraveling it arises from the fact that it is arranged to serve multiple purposes; the first half (Chapters 1-8) is mainly historical record up to the discovery of the organizer but also covers the stages of development in sequence; the second half concerns the variety of later findings together with his final theoretical position. Another significant feature, which makes it exceedingly laborious to follow Spemann's arguments thoroughly, is that the book lacks any subject index. For this reason I attach to my following analysis of his arguments a number of the most relevant page references. Horder and Weindling (1986, Note 55) have already provided a list of references to Spemann's scattered discussion concerning the two components of the organizer mechanism.

Within a year of the 1924 paper Spemann's emphasis has indeed shifted; *"It.... seems probable that in normal development the differentiation of the medullary... (neural)... plate is determined by the underlying ento-mesodermal layer"* (Spemann,1925, p. 501). By this time Marx had performed the conclusive experiments earlier proposed by Spemann; he had implanted archenteron roof directly under gastrula ectoderm and shown it to be sufficient to induce neural plate. Further evidence (particularly exogastrulation (Fig. 4)) is reviewed in EDI (e.g. Chapter 8, which is mainly devoted to *"the share of"* mechanisms and *"general dependence.. (of neural plate)..on the mesodermal substratum"*). *"The origin of the medullary plate out of its normal material ...has been the object of numerous experimental investigations with the aim of ascertaining the role played in normal development by the inductive faculties of the mesoderm ... The presumptive medullary plate... was determined into medullary plate merely by the influence of the underlying mesoderm"* (EDI, p. 170)[40]. However, there is no question but that Spemann maintained his original dualistic viewpoint and would do so until his final statements on the subject. In the above quoted 1925 paper he adds, referring to the field mechanism acting in the mesoderm; *"(i)t would appear that such a secondary embryonic anlage... (i.e. neighbouring cells of the ento-mesoderm)... is induced by some superior power"* (p. 501). Chapter 8 (p. 190-8) shows that he still wants to retain the possibility of field mechanisms in neural determination by the organizer. By 1927 he had bolstered the dualistic position in theoretical terms by introducing the notion of *"double assurance"*[4]. Regarding a *"decision between these two possibilities, ...(they)... need not exclude each other"* (EDI, p. 147). It is important to realize that Spemann did not see the two mechanisms as in conflict; on the contrary they were complementary and mutually supporting, and both are seen as products of the organizer. In invoking the principle of double assurance he usually recalls the lessons he learned from studying the lens - from this earliest stage of his work on the eye he had a dualistic perspective - and his discussion of it occurs in a chapter on the eye (EDI, 92-97). *"Our knowledge of the development of the vertebrate eye has from the beginning taught us to be cautious"* (p.170).

Among the earliest scientists to begin their own experimental follow-up to Spemann's discovery, and certainly the first in the UK, was Julian Huxley. Around 1925 he began experiments designed to verify a Childian interpretation of amphibian gastrula organization[41]. As for Spemann's initial intention (all discussed already in the 1924 paper) this was to explore what he called the *"structure"* (H, p. 60-1) of the organizer; *"the implanted organizer would have a definite structure of its own. On this would depend.....its determinative effect"* (SM, p. 175). What he meant by this gives us an indication of how he actually envisaged the nature of the organizer. Polarity, extent (size) and orientation of the secondary embryo might all be ascribed to the influence emitted by the organizer. (In a sense he almost treated the organizer as "the embryo in miniature"[42]). He proposed (in the 1924 paper) that these features could be investigated by examining the effects of subdivision, rotation, or by simple mechanical disorganization of the organizer. Although Spemann had suggested examining the effect on the organizer action of killing the graft tissue in 1924 (EDI, p. 225), he delayed doing so. Others (particularly Holtfreter, now in Berlin) were left to bring this new approach to the fore (H, pp. 93-101, 137-43). The first "killed organizer" experiment was attempted in 1929, and the results published in 1932. This heralded an abrupt change of emphasis.

With the discovery that the organizer effect could be brought about by a "dead organizer" graft, *"physiological chemistry took possession of the field"* (EDI, p. 222). Chapter 11 deals with this phase (its history summarised in p. 225-30). There followed a hectic, but brief, period in which a number of groups attempted to identify the nature of the organizer in chemical terms (see Needham, 1942; Saxén and Toivonen, 1962). By around 1929 Waddington had been attracted by news about the organizer to start his own embryological work. He soon teamed up with Needham, who was ideally placed to bring to bear the major movements in biochemistry and the study of biological molecules then centred on Cambridge (see Needham 1931; Olby, 1986). Needham was naturally drawn into this work, fresh from completing his immensely authoritative three-volume "Chemical Embryology" (1931). Enthusiasm did not last long and eventually turned into disillusionment (H, p. 137-143). Initially the Cambridge group argued that the organizer was a steroid. "...we always thought primarily in endocrinological terms" (Needham, 1968, p. 281), later turning to consider metabolism and respiratory rates. A seemingly endless list of disparate (and often inorganic) chemical agents having effects on embryo cells recognizable as inductions began to emerge (variously dubbed "unnatural", "abnormal" or "heterologous" inductors; discussed EDI, p. 230-246).

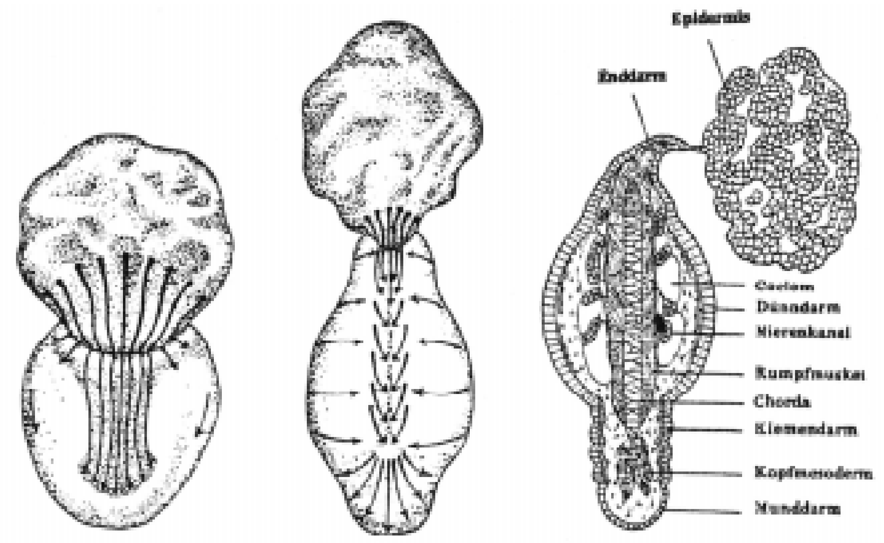

Fig. 4. Exogastrulation. *Under certain culture conditions, the early gastrula undergoes evagination movement (shown [left] through two stages by arrows) in place of the invagination of normal gastrulation. As a result, ectoderm (above) develops and differentiates (shown right) - without forming neural tissue as normal - independently of the separate mesendodermal mass (below). The phenomenon demonstrates the normal dependence of neural tissue on induction by the mesendoderm. It also illustrates large scale cell movements and "self-organization" of separated parts. From; Holtfreter (1933) W. Roux. Arch. EntwMech. Org. 129: 670-793.*

The message increasingly apparent from the chemical approach was that inductors (normal and abnormal) were non-specific in nature and had a primarily "permissive" (as opposed to "instructive") action in activating the reacting tissue; nor (because the chemical agents - many with no possible connection with normal biological mechanisms - themselves lacked organization) did they seem to provide any basis for the impressive spatial organization sometimes evoked in responding tissues. This would not have come as a complete surprise to Spemann. As Chapter 10 makes clear, even before the chemical results, examples of the action of "abnormal inductors" had already pointed to similar conclusions (a particularly challenging example being the "homeogenetic" induction of neural tissue by neural implants, discovered by Mangold in 1927 (EDI, 214-5)). Moreover, Spemann had regarded induction as a "release" rather than instruction from 1921[43]; *"(F)rom the beginning the question was raised: what is the share of the action system and the reaction system in the origin and the character of the induction product?". "In the experiments undertaken to solve this problem the share of the reacting system turned out to be greater and greater and eventually so great that the organizer concept itself* *became problematical"* (EDI, H, p. 141). As the emphasis shifted towards the reacting tissue, it became increasingly important to define the potentialities within that tissue; a complex terminology resulted, including "competence", "reversible determination", *Bahnung*[2].

Out of their intense involvement with these developments Waddington and Needham arrived at their own terminological system defining the role of stimulus and response. Based on the often rudimentary differentiation of neural tissue induced by chemical agents, they distinguished the direct effect of the inductive stimulus ("evocation")[6] which only achieves generalized neural differentiation, from "individuation" in which regional patterning (i.e. specific parts of the nervous system) also occurs. This second aspect reflects potentialities and interactions within the responding tissue itself, in other words a field process. Waddington's particular way of characterizing the key problem in this way was later to have interesting repercussions, especially in the UK. I will return to this theme in later sections.

Through the second half of his book Spemann builds up the evidence, not just for the crucial involvement of the responding tissue, but also for its ability to generate organizational complexity autonomously. Chapter 12 ("The Time Correlation of Induction") introduces Vogt's concept of "*Bahnung*"[2], whereby the responding tissue limits its receptivity during different developmental stages; by contrast the stimulating fields remain operative long-term and even in adult tissue (i.e. in regeneration; see p. 313-317). Chapter 13 deals with "Regional Determination". In 1927 and 1931 Spemann (following up earlier suspicions) showed that specific regions of the archenteron roof induced specific regions of the neural tube. In addition to showing the ability of parts of the neural tube to self-regulate and self-organize this finding also importantly showed a degree of (instructive) specificity of neural inductors after all: not everything was left to the responding tissue! Chapter 14 ("Complementary and Autonomous Induction") returns to issues of assimilation - now such phenomena seem to be subsumed under the umbrella term "complementary induction" - but the main point of the chapter is to emphasize the mounting evidence for the ability of responding tissues to autonomously generate considerable complexity without requiring any structural contribution by the inductor. *"Almost the whole complication must lie on the part of the system of reaction"* (p. 369). All these chapters point towards the importance of the potential for autonomous organization (i.e. "harmonious equipotential system" properties) intrinsic to responding tissue. The culmination of all these lines of evidence is reached in the chapter that then immediately follows, entitled "The Embryonic Field".

Once again, with the new emphasis that is now placed on "fields", we are confronted with difficulties involving terminology. It is often unclear in Spemann's later chapters whether one can detect *any* distinctions between "induction", "organizer" and "field"[44]. But Spemann gives a number of reasons for using the new term. *"The conception of the embryonic field offers itself as a convenient means to comprehend the various facts of induction, especially the more complicated ones"* (EDI, p. 303). *"(W)hen we deal with the phenomena of regional determination, of autonomous induction, and of protracted and overlapping fields, that conception facilitates the description of the facts"* (p. 305). *"(A) conception that seems to be useful in the comprehension of these important and remarkable phenomena"* (p. 296). *"The different phenomena of induction, of determination in accordance with place and region, may be brought under a conception which has been taken over from physics"* (p. 297). *"(T)hese fields have no sharp limits like the tesserae of a mosaic; rather they constitute a pattern with indistinct borders"* (p. 309-10). *"(T)he whole larva, even of later stages, is permeated by embryonic fields which become manifest as soon as a piece of reacting material has been brought under its influence"* (p. 309). Other than in these statements Spemann offers no other rationale. However he provides further clues about his underlying conceptualization when he briefly discusses how fields are set up, interact and are sub-divided. He envisages new sub-fields emerging through competitive mechanisms, "rivalry" and by "limiting each other" (p. 311) or by "mutual inhibition" and "interference" (p. 310) and dominance (p. 311)[45]. Induction is just one contributing factor within the overall, multidimensional field effect (p. 304). Figure 161 perhaps comes close to depicting how Spemann actually saw fields operating (Fig. 5).

Spemann sought to distinguish fields (Chap.15) from gradients, which are given a full and critical treatment in Chapter 16. In 1930 Spemann had been specifically challenged by Huxley (in a short letter in *Naturwissenschaften*, translated into German by Spemann) reminding him of his 1924 attempt to interpret the organizer in terms of Childian gradients. Huxley called into question the meaning of the most critical aspects of terminology by insisting on the combined term "gradient-field". This challenge was even more evident in Huxley and DeBeer's substantial book of 1934. This was the first available, detailed account in the English language of Spemann's work. The issues were presented with a never-to-be-surpassed coherence and the organizer was discussed as if it had all but solved the entire problem of embryology. While acknowledging Child's influence, Spemann is distinctly critical of Child's theory, and of Huxley's contribution. *"The work of Child and his associates extends through several decades and has been communicated in numerous publications"* (EDI; p. 321). *"It should not be forgotten, however, that... (the gradient theory)... in its entirely general form would scarcely have gained the importance it possesses at present, if Child, from his particular point of view, had not devoted many years of thorough study to this question"* (p. 345). He lists (p. 330-2) the difficulties he sees in gradient theories; they are "arbitrary" (p.325) and an "over-simplified explanation" (p. 329). He points out that the mere existence of a graded property does not prove its causal role; its existence may be coincidental or consequential (p. 326). He questions how a multiplicity of discrete states can be generated from a singularity (p. 326); *"Bautzmann ...has called attention to the difficulty that it is hard to understand how qualitative differences may arise from quantitative ones in the different regions"* (p. 331). *"Another difficulty seems to lie in the fact that the gradient ......must be conceived as continuous, whereas the series of formations whose differentiation would be determined by that gradient...is absolutely discontinuous"* (p. 331). *"(T)hese differences in growth.... (all the bulging-out and doubling-in which plays so eminent a role in the molding of visible form).... are so various that they could no longer be derived from one single gradient"* (p. 330).

However, Spemann's final position on gradients is ambivalent and not unsympathetic. He quotes Boveri's gradient concept with approval. At times he seems to equate fields and gradients and in his own conception of fields he often uses the idea of a gradient of influence spreading from a dominant centre (see SM, p. 181-2; EDI, p. 371). *"In its attempt to relate the part to the whole, the gradient theory no doubt exerted its influence on the organizer theory, with which it overlapped to some degree, as Spemann*

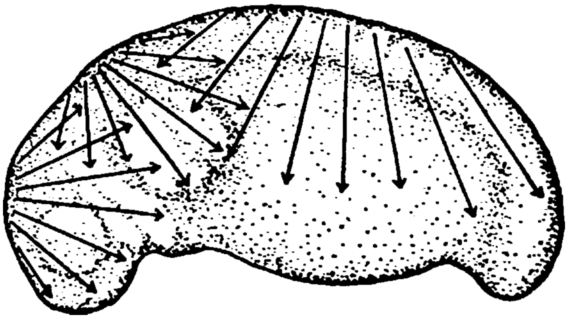

Fig. 5. A depiction of embryonic fields. *The arrows indicate the radiating "field" action organizing pattern in three overlapping sub-fields. This diagram was included in Spemann's 1938 book as Figure 161. (Originating from Holtfreter (1933) Biol. Zentralbl. 53: 404).*

himself realized. It still today remains one of the few general unifying concepts that attempts to account for overall pattern in the development of the organism as a whole" (Willier and Oppenheimer, 1964, p. 129). *"It is, of course, the peculiar position of the gradient hypothesis that it is the only concept so far found which covers the outstanding phenomena of development and regulation, but that it is exceedingly difficult to devise or perform experiments to prove its validity satisfactorily"* (De Beer, 1937, p. 983).

Commentary: It is evident that by the end of his book Spemann's original conception of the organizer remains essentially intact, even if, in a shift from the balance between the two mechanisms of the organizer suggested in his original presentation, neural plate formation was now effectively attributed to mesodermal induction alone. Certainly the facts revealed in the original 1924 observations had in no way been questioned and the demonstration of embryonic assimilation that they so compellingly provided had lost none of its impact or importance; "(T)he conception is still in conformity with the facts" (EDI, p. 368). The establishment (particularly by the chemical evidence) of the restricted role played by the inductive stimulus (together with the increasing evidence for the potentialities for self-organization of responding tissues) meant that the second of Spemann's original organizer mechanisms (the field-mechanism) was now effectively re-endorsed; induction itself became subjugated to the new field-based perspective.

The field concept was introduced specifically to "explain" and accommodate the various new, complex, dynamic and regulative phenomena met with in embryonic systems. A number of Spemann's contemporaries tried to define the concept in more precise and formal terms (e.g. Gurwitsch, Weiss, Bertalanffy, Huxley) but it is hard to avoid wondering how the field concept adds materially to Driesch's "harmonious equipotential system". Spemann says as much; Driesch's "equipotential system capable of harmonious differentiation still remains as a real problem....Attempts to solve this problem, partly logical, partly experimental, induced several investigators to introduce into experimental embryology the conception of the "embryonic field"" (EDI, p. 347-8). However one new element was being introduced as the idea of fields was increasingly adopted. Starting in 1927 Spemann in collaboration with Otto Mangold had shown that neural induction involved "Regional Determination". Rostral and caudal parts of the archenteron roof selectively induce specific (rostral or caudal) parts of the nervous system, thus showing that neural development is partitioned into several regions. From around 1924 (as he began to relate his lens work to neural induction) Spemann had introduced the notion of inductive chains or hierarchies; "one may ..imagine development as composed of shorter or longer "chains of successive inductions" the links of which would be inductors or organizers of rising orders" (primary, secondary, tertiary) (EDI, p. 167). Although little further detail is available, one can infer (as seen in Figure 161) a conception in which organ- or region-defining sub-fields emerge secondarily within the initial single field set up by the primary organizer.

There is an additional source of valuable insights into the origins and nature of Spemann's overall conceptualization in the contents of Chapter 5, which deals with the role of the formative movements ("dynamic determination") of gastrulation and neural plate folding in relation to the differentiation of cells ("material determination"). The approach discussed here derives primarily from the experiments of Walther Vogt (and his associates, von Ubisch, Goerttler) in Munich[46]. Although Vogt is now best known for his somewhat later detailed studies of amphibian fate maps, he was influential by 1924 because he argued strongly for the establishment of pattern before gastrulation, and therefore before the organizer comes into play. He showed (1922-3) that isolated fragments of early gastrulae underwent autonomous and characteristically distinctive patterns of morphogenetic behaviour and tissue movements, from which he inferred their "dynamic determination" (EDI, p. 101-5). Chapter 5 shows just how seriously Spemann took these issues. Vogt, and particularly Goerttler, then argued that visible differentiation of larval structures ("material determination") was a secondary consequence of dynamic determination; in other words differentiation was causally dependent on prior morphogenetic patterning. Quoting Vogt's 1923 description of his conception extensively and admiringly ("This conception of development has been expressed so beautifully and clearly", EDI, p. 125), Spemann implies that he shares much the same perspective.

There is a sense in which Spemann's whole approach is one that collapses the complexity in time and space of the epigenetic events involved in embryogenesis. He is primarily interested in the finally developed pattern of the larva as a finished, elaborated, organized whole. Moreover, in accordance with his earliest expectations and research interests, he tries consistently to relate and refer the final pattern as directly as possible back to the egg stage. His perspective has features akin to a "promorphological" one in which pattern is implicit in the earliest stages. (His earliest studies involved a gradual shift from an essentially

Fig. 6. Walther Vogt

preformationist position to one that increasingly recognised the attainment of cell commitment only at late (gastrula) stages). He seems to envisage, as we have indicated, an emergence of initially overlapping sub-fields out of primary fields by lateral, internal interactions within the plane of the field. With such perspectives the complexities of intervening epigenetic events (e.g. processes like tissue migration or folding) become almost an irrelevance. Indeed it is interesting in this context to consider how Spemann deals with the various phenomena of morphogenetic cell movement. One gets the clear impression that he has detached such matters from the central problem at hand, that of pattern formation. The issue has become hived off and left behind within an early chapter (Chapter 5) and in so far as it is returned to at all in the later parts of the book, discussion is mainly limited to repeating how Goerttler's claims on the role of movement have effectively been refuted (EDI, p. 190-8, 204-8)[47]. Fate maps of course provide the most obvious evidence for the importance and scale of cell movements, but, as we have already come to suspect, such concerns were apparently of subsidiary interest to Spemann; he hardly mentions them at all and after 1924 only returns in passing to correct or discuss his earlier inconsistencies concerning the fate map of the neural plate[34].

How were Spemann and the organizer perceived by observers by the time of the war? "Organizers have come into prominence through the dramatic manner in which they have demonstrated epigenetic development....... Their most striking action, still veiled in mystery, lies not in the induction of a particular organ here or there, but in making plastic material form a harmoniously constructed embryo" (Harrison,1937, p. 12). This was all the more significant because his discovery came "at a time when the tendencies of thought were in the direction of preformation" (Harrison, 1937, p. 12). Needham also identified the revelation of the potential of epigenetic mechanisms as explanations of embryogenesis as the most important message from Spemann's work; "The essentially new thing in Spemann's conception of the organisation centre or Organiser was that it set the process of *Dependent Differentiation* right at the heart of normal development" (Needham, 1942, p. 103). On the other hand there was some implied criticism; "The use of the term "organizer" is likely to be attended by some confusion, for the word may be readily taken to imply more than we are really justified in attributing to the thing itself" (Harrison, 1933, p. 317). "Since the word "organizer" connotes a master regulator which created organization, and since there are in the course of development many actions of the same general character that could hardly be accorded such a role, it is perhaps more appropriate to use the word "inductor" to denote processes of this kind" (Harrison, 1969, p. 29). In a 1935 review Paul Weiss, an early field theorist, makes his concern with words obvious; its title refers to "the so-called organizer" (Weiss, 1935). His textbook of 1939 covers Spemann's experiment in some detail; it "undeniably has been one of the major achievements of modern embryology (Weiss, 1939, p. 345). But he then asks "Is the "organizer" an organizer?" Terms have "often been mistaken as to their implications" (Weiss, 1939, p. 346). "The term "organizer" thus turned out to be a misnomer" (Weiss 1950, p. 178). Child is dismissive of both the concept and the word; "inductors and organizers are, then, nothing new but are simply cases of physiological dominance.... it is perhaps desirable to drop entirely the term "organizer" (Child, 1941, p. 10). Spemann may well eventually have shared some of these concerns connected to his choice of word; towards the end of his book he too sometimes uses the word organizer in quotation marks.

Spemann's book is most frequently remembered for one passage above all; in the closing paragraph Spemann asserts "my conviction that the suitable reaction of a germ fragment, endowed with the most diverse potencies, in an embryonic "field" its behaviour in a definite "situation", is not a common chemical reaction, but that these processes of development, like all vital processes, are comparable, in the way they are connected, to nothing we know in such a degree as to those vital processes of which we have the most intimate knowledge, viz., the psychical ones" (EDI, p. 372). We know that Spemann insisted on retaining this passage in translation (HW, p. 202). It echos the last sentence of the 1924 paper in which he refers to "all those enigmatic peculiarities which are known to us only from living organisms" (SM, p. 183). Spemann's statement is open to easy misinterpretation, and all the more so because of the obscurities added through translation. The psychic analogy, on which the passage leans so heavily, is perhaps one that we now find impossible to engage with. But Spemann was brought up on it, and constantly used as a way of identifying what he saw as the features in developing systems most needing to be explained, e.g. integrity, wholeness, complexity, response to complex stimuli. Referring to the problems of "wholeness", he regrets that "we have as yet no real conception of what this means in the language of physiology" (EDI, p. 366): the "language of psychology" was all that he could turn to. There is ample evidence throughout his book that Spemann is, while fully aware of past interpretative aberrations, knowingly concentrating on the challenges presented by whole, intact, and therefore living, organisms, but also that he is only prepared to draw conclusions on the basis of hard evidence. It would be quite out of character and context to read Spemann's final paragraph as any sort of plea for vitalism[48]. The evidence suggests that it is an assertion, in the only way he had available, of a position akin to organicism.

1.3 The rise of Cell and Molecular Biology; 1940-1965

With the coming of the World War the classic era of experimental embryology that one associates so closely with the Spemann tradition underwent a disillusioned collapse. *".... by the middle of the century the resources of experimental embryology were pretty much exhausted"* (H, p. vii). Not only did Spemann himself die early in the war, but many among his school of associates emigrated and dispersed (Hamburger, Schotté, Holtfreter, Glücksohn-Waelsch, all went to the USA). All of the emigrés changed their research interests away from working specifically on the amphibian organizer. At that same time Needham abandoned his embryological work. Waddington had already spent time in the USA switching his interest to *Drosophila* genetics. As he put it, "All those of us who discovered "unnatural evocation" very quickly dropped the subject and went on to something else" (Waddington, in Needham, 1968, p. 286); *"Most of the workers who had started with the biochemical approach, and found themselves gazing down into those impenetrable depths, thought discretion the better part of valour and turned their attention to other possibly more manageable problems"* (p. 286). *"The phenomenon of embryonic induction, which has been a focal point of interest to so many embryologists, has lately somewhat faded out of view"* (Holtfreter, 1948, p. 17).

The prevailing approach to embryology was changing; and by 1970 would be greatly different. Oppenheimer sums up trends as follows; *"The concept of organizers as such gradually dissipated, and the word if used at all today would be found in out-of-date textbooks" (*Willier and Oppenheimer, 1974, p. xiv-v). *"In the years since (1941), references to gradients have proliferated in the literature but still have received no real explanation.....analysis of fields and of most gradients has defied manifold efforts, and recently has not been a popular area of investigation"* (p. xv). Needham also sensed the shift of interests; *"The intellectual climate of biology in 1965 is so completely different from what it was twenty-five years ago that there is little point in any attempt to revise* Biochemistry and Morphogenesis*"* (Needham 1968, p. 278). Holtfreter blames one particular factor; *"During the past few decades, interest in the problems of induction has faded away. The probable reason is the failure of the workers in this field to chemically characterize the nature of the naturally occurring inductive agents"* (Holtfreter, 1991, p. 126). But there were many factors at work.

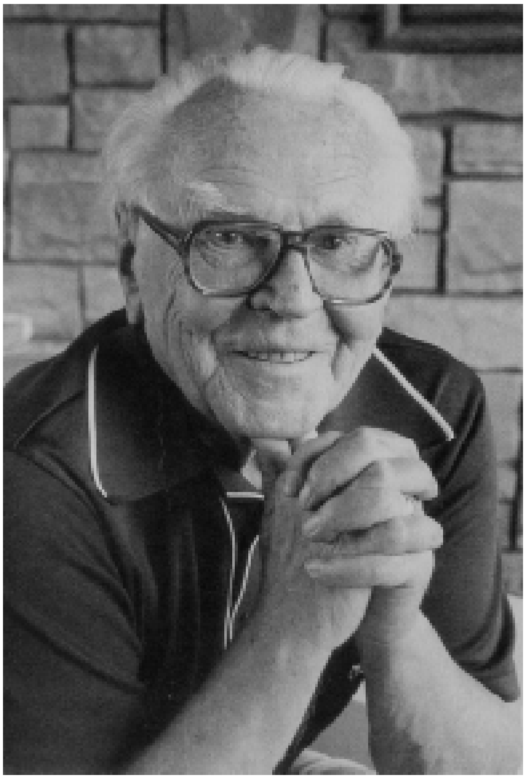

Fig. 7. Johannes F.C. Holtfreter (1901-1992). *Reproduced with permission from Academic Press.*

The philosophical heart-searching of the 1930s had effectively resolved itself; now vitalism was generally discounted. As symbolized by manifestos such as Schrödinger's "What is Life" (1942), it was becoming widely accepted that all phenomena in the biological realm could potentially be explained in reductionist, physical or chemical terms. Now Woodger (1948) critically highlighted the conceptual deficiencies of the subject and called for a thorough theoretical overhaul, especially concerning the problems of "levels of analysis" and terminology, themes often to be repeated (Weiss, 1950, p. 177-8; Waddington, 1966, p. 105). The reductionist trend would hasten the marginalization of embryology as a coherent, mainline subject within biology. In the post-war period the rest of biology was moving on at a rapid rate. Explanations for biological phenomena were sought in "cell biology" and then increasingly in "molecular biology". *"In 1925, the organizer was in its heyday: today it is spoken of principally in historical connections, and sometimes disparagingly. Cells are very popular in 1970"* (Oppenheimer, 1970, p. 75). *"It was inevitable that a forceful assertion of reductionist trends would shake its foundations. Indeed the radical shift of emphasis to the cellular and subcellular levels, and, from the 1950s on, to the molecular level, transformed experimental embryology to developmental biology. The brilliant successes of molecular biology drew developmental biology into its orbit"* (Hamburger, 1988, p. vii). Leaders of the trend included Holtfreter, Abercrombie or especially, though he is now largely forgotten, Paul Weiss, whose speculations on the theme of "molecular ecology" were very influential. Now research topics of interest to developmental biologists included cell-cell communication, cellular re-aggregation, mitosis and its control, cell adhesion and selective affinity, cell locomotion and migration (e.g. neural crest), extracellular matrix, cell membranes, cell death and so on. Many of the new developments followed on from the arrival of new techniques, such as electron microscopy, radio-labelling and cytochemistry (Oppenheimer, 1966). As embryology became more techniques-based, workers tended increasingly to concentrate on single ("model") organisms or on single organ systems (feathers, limbs, somites, crest, etc). The result was the creation of subspecialities within the discipline and fragmentation. It inevitably became more difficult to maintain an integrated view of the central problems of the subject.

Waddington is a particularly interesting and influential figure throughout this period. His contributions exemplify many of the features just referred to, including a certain lack of focus, which in his case reflects an astonishingly broad range of interests. His important book *"Principles of Embryology"* (1956) well illustrates the trends (e.g. the emphasis on cells, differentiation, plasmagenes, the relating of genetics to embryology). He defines his agenda as follows; *"during the last decade or so it has become increasingly clear that something further is required... (over and above the approach of the twenties and thirties).... The time has come to find some point of view which will suggest methods of attacking the problems of the nature of the interactions between ooplasms and nuclei, and between inducing and induced tissues or the different parts of a field. Broadly speaking, two main new approaches are being developed at the present time: one which is biochemical and cell-physiological, another which is genetical"* (Waddington, 1958, p. 18). The emphasis on genetics is marked. Genetic factors are linked primarily to matters of cellular differentiation. Although the first half of the book is arranged (in the traditional comparative and descriptive manner) by species, the large theoretical, second section reflects Waddington's fundamental division of developmental phenomena into cell differentiation and individuation (which is further subdivided into "pattern formation" (or "regionalisation")[15] and morphogenesis[12])[49]; these three categories are sharply separated from one another in the two final, integrative chapters. Fields are discussed in a separate section, but induction (and the chemistry of induction) is not. And yet a tally of references to leading concepts in the subject index reveals how induction pervades the book; organizer, 18 page references; gradients, 10; fields, 15; induction, 46. Induction is a constant, and unquestioned, issue throughout the book.

By around 1970 the emphasis on cell biology was far advanced. This is easy to document through examination of available textbooks. In 1951 Holtfreter had noted that no textbooks had been written on experimental embryology over the preceding ten years. By the late 1960s there was a wealth of new texts - typically including "developmental biology" in their title in place of the earlier term "embryology" and notable for their enthusiastic extension into new cellular topics (e.g. Sussman, 1960; .Barth,1964; Ebert and Sussex, 1965; Saunders, 1970; Gurdon, 1974). Now molecular biology of the cell occupied considerable portions of the coverage and some classical embryological topics were abbreviated or displaced. Moreover the wide range of topics covered (organogenesis, comparative embryology, cell differentiation, genetics, regeneration, endocrinology, evolution, aging and so on) meant that it was even harder to maintain any sense of coherence or centre. Deuchar's "Cellular Interactions in Animal Development" (1975) does not even name the "organizer".

One, obvious, effect of Spemann's legacy was to focus attention on neural (or "primary") induction. Continuing interest in the chemistry of induction concentrated almost exclusively on this one inductive situation. Efforts chemically to identify the inductor continued, particularly from new groups in Finland, Belgium and Japan. All ended up arguing for some form of gradient theory (see H, Chap. 9). Gradients were, presumably, preferred over fields because they offered greater prospects of identification. Saxén and Toivonen reviewed the subject thoroughly in 1962 and commented; *"Despite the many noteworthy results achieved during this most recent period of active study the problem still remains open, even in some of its most essential aspects"* (Saxén and Toivonen, 1962, p. ix). Terminological chaos still constantly threatened (Dalcq, 1957). And by 1978 leading participants concluded that *"progress in understanding embryonic induction has been slow. Communication between cells during primary embryonic induction is far from being described in molecular terms"* (Nakamura, 1978, p. 315). For developmental biologists more widely, neural induction had become a surrogate for studying the whole embryo, and this one system had almost come to stand for all known inductions. Moreover, induction had perhaps come to be identified with the issue of chemical factors to the exclusion of other problems or considerations.

Of Spemann's immediate successors in the study of induction and the organizer the most important was Holtfreter and it is interesting to examine the extent to which he further modified the earlier concepts. Holtfreter and Hamburger's significant article in "Analysis of Development" (1955) (along with Holtfreter's shorter pieces in 1951 and 1968) was the nearest to an authoritative statement on possible revisions to Spemann's theory. They emphasize the newly recognized complexities of developmental interactions. *"Differentiation...proceeds through the mediation of several generations of properly distributed inductors which succeed each other and may combine in various ways to act as coordinated determinative systems"* (HH, p. 256-7). *"As Harrison (1933) has emphasized long ago, determination of a primordium is not necessarily a final one. Here we see that it may occur stepwise..... (Matters) become still more complicated by the fact.... that a single component of an inductor system may have dual or multiple effects...... All these data taken together give quite a puzzling picture of the problems of induction. But these complexities deserve to be emphasized because they have been neglected too often by those writers who believe that "the" induction problem can be understood on the basis of a single unitarian hypothesis dealing with a system of gradients which encompass the whole embryo"* (Holtfreter, 1951, p. 129-30). Some emphasis is put on the concept of "self-organization" (HH, p. 281). One source of difficulty in the analysis arises from the fact that both inductor and responding tissues are seen as having field properties, so that both elements in the situation "defy further breakdown into localizable subunits" (HH, p. 279). The focus is, however, most definitely on the phenomenon of induction in its own right and now the word is clearly distinguished from earlier usages. *"Since the term "induction" has sometimes been used in a loose way, let us try to circumscribe it.....inductive stimuli operate only at certain stages....during early development...they are normally ineffective unless there is an intimate contact between inducing and reacting tissues. The effects of the inductive tissues are undeniable, since in their absence none of the ectodermal and probably few of the mesodermal differentiations would ever arise...... "inductors" are ... embryonic tissues which determine the* cytological *fate of the reacting adjacent cells"* (p. 275).

Regarding the "organizer" a defensive, and seemingly critical, view is detectable. Holtfreter and Hamburger remind us that the term, which they print within quotation marks, was from the start *"provisional"* (HH, p. 244). It has "suffered further devaluation" (p. 280). "It would be entirely misleading to conceive of the "organizer" material as of a kind of general manager" (p. 279-80). It is just another field involving behaviour "essentially like dead or adult tissue" (p. 180). Holtfreter and Hamburger seem ultimately to rely in the same way as Spemann did on fields; their concept of "self-organization" is operationally indistinguishable from a field concept (Fig. 8). *"To conclude, then, the "organizer" has the characteristics of a morphogenetic field which is, however, not really harmonious equipotential in the strict definition of Driesch, and it induces another, or several other, fields which are likewise capable of regulation and of self-organization"* (p. 281). Although they clearly try to draw a distinction between induction and fields, Holfreter and Hamburger remain in much the same dualistic position as Spemann (p. 279)[50].

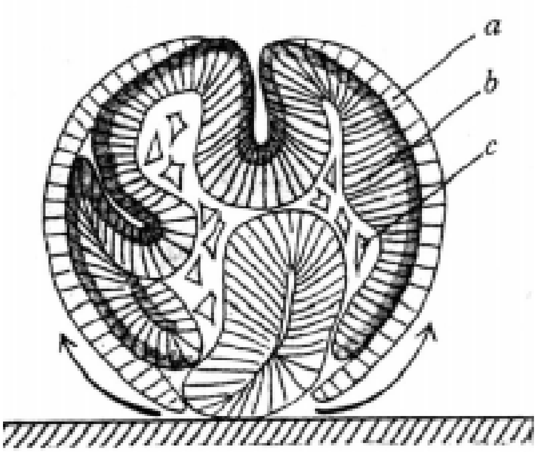

Fig. 8. An example of "self-organization". *A single cell sheet of gastrula ectoderm was isolated in culture medium, resting on a dead organizer. Various forms of morphogenetic cell movement occurred autonomously to create a complex pattern; some are indicated by arrows [identifying movement of cells outwards to form new outer cells (a) covering earlier outer cells (b)]; in other regions folding and invagination has formed discrete structural elements, probably including neural tissue. Mesoderm has also differentiated (c). From Needham (1942), Figure 81; based on Holtfreter.*

Do Holtfreter and Hamburger relate morphogenetic cell movements to these themes? Here is what they have to say on the subject; *"(M)uch emphasis has been placed upon the phenomenon of induction, but other, equally important principles of organogenesis... (include)... the importance of morphogenetic movements and self-organization, ...selective cell adhesion; structural, mechanical, hydrostatic factors in development....phenomena of differential growth"* (HH, p. 275). *"(I)nauguration of a new trend of differentiation... (e.g. through induction).... is almost invariably associated with new trends of* kinetic *activities of the induced cells, such as invaginations, delaminations, new rates of cell division, etc."* (p. 275). But on the question of how the themes are actually linked together they are notably brief. Inducing and responding tissues *"must be interlocked in space and time in order to insure normal development. This is principally achieved by directed cellular mass-movements"* (p. 276). *"As a rule, inductions are associated with other phenomena such as directed cell movements, invaginations, delaminations, etc and with new and tissue-*

specific rates of cell multiplication of the induced cells" (Holtfreter, 1951, p. 118). *"The essential mechanism which brings about and controls this coordination.... (of inductive and responding tissues) ...are the morphogenetic movements: they normally unite the acting with the reacting tissues at the proper stage and site of the organism"* (Holtfreter, 1951, p. 134). In his final review Holtfreter still has only this to say; *"If inductive processes may be regarded as the principal device by which the vertebrate embryo acquires its diverse cytodifferentiations, then directed movements of cells and cell masses is perhaps the most important and ubiquitous device by which the anatomical body plan.... (comes).... into being. In embryogenesis, ...induction and morphogenetic movement.... operate in alternating cycles"* (Holtfreter, 1968, p. 14).

Waddington was clearly very exercised by the concept of fields. He reviewed it in detail on many occasions (1934, 1940, 1956, 1966b, 1968, 1972). *"In spite of all the work that has been done on the regional determination of the neural plate, we still find ourselves forced to appeal to the mysterious process of "self-individuation" to explain the appearance of pattern"* (Waddington, 1956, p. 467). *"Most of the earlier writers who employed the field concept seem to have considered that eventually it would be found that the effective causal basis for the processes going on within the field is the distribution of one or a very few morphogenetic substances"* (Waddington, 1966b, p. 111). *"I have gradually come to feel that this difficulty, of deciding what the field is a field of, does not have quite as much importance as I once thought"* (p. 108). *"Even in the 1930s when ...(the problem of fields and gradients).... was a relatively fashionable subject, it was one that I personally always felt very wary about, and little has happened since then that would encourage one to feel much bolder in tackling it. The notions of fields and gradients have always been theoretical concepts...."* (p. 105). Needham expresses similar disappointment; *"Looking back now, I think we were perhaps unduly influenced at that time by the field concept, which so far may not have proved as fertile heuristically in biology as it did long ago in physics"* (Needham, 1968, p. 287). *"The weakness of the embryological field theory is, I now think, ...because there are so many different embryological fields"* (Waddington, 1966b, p. 108). The field theory as earlier conceived was a "very drastic abstract simplification of the true situation" (p. 110-2). Whereas in 1956 the problem had been perceived as due to terminological confusion (Waddington, 1956, p. 23-8) now, faced increasingly with the complexities in the experimental evidence, Waddington saw fields as a methodological issue. What was required was a "technique of analysis". He saw the solution in terms of "the temporal characteristics of fields" and advocated "topology" as a method that could handle the multidimensional problem that is at the heart of development (Waddington, 1966b, p. 109; 1972, p. 139).

Child's continuing influence is evident throughout the reviews of Weiss, Waddington and Holtfreter, who all express their reservations about gradients. *"The double gradient theory of Dalcq and Pasteels (1937...) follows similar lines.... (to Child's).. That qualitative differences between the (graded) inductors are due to different concentrations... It is based on assumptions which seem to be controversial or arbitrary, and some of the interpretations offered are merely circumscriptions of the problems to be solved..... In most instances when this concept has been applied to certain observations, other hypotheses would serve as well, if not better. It seems that too many unrelated, though partly overlapping processes are engaged in embryogenesis to allow for their unitary interpretation in terms of an oversimplified gradient concept"* (HH, p. 283). As Holtfreter had already said; *"this reviewer has little confidence in the endeavours of some workers who have tried to attribute all the complexities of the initial steps of embryogenesis.... to the graded action*

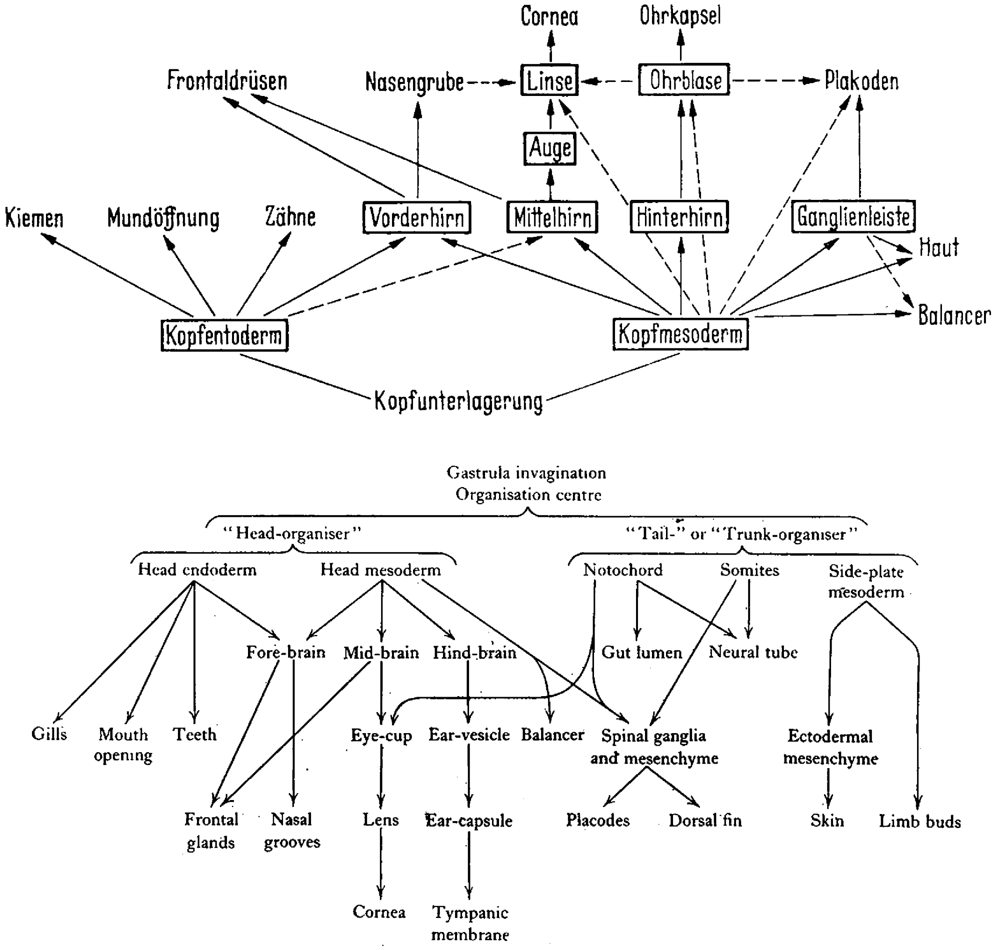

Fig. 9. Early representations of the notion of the epigenetic cascade. *These diagrams summarize the expanding series of known chains of sequential causal (including inductive) events through which an increasingly elaborate array of differentiated structures is gradually built up, starting from the primary organizer (above in lower diagram) or from the head mesendoderm (in upper diagram). Above; from Holtfreter (1938) W. Roux Arch. EntwMech. Org.138: 522-656. Below; from Needham (1942).*

of one or two hypothetical substances which are assumed to pervade the whole embryo along gradients of concentration. ....Any physiologist would shrink from the task of searching for such an omnipotent master compound" (Holtfreter, 1951, p. 145).

Commentary: The period between the war and Wolpert's introduction of positional information in 1968 can perhaps best be characterized as one of a fragmentation in developmental biology, led particularly by an absorption increasingly in detailed cellular and molecular mechanisms. After the comprehensiveness of Spemann's book, little appeared to have changed as regards the classical issues. Certainly the duality within his concept of the organizer was taken largely for granted[50]. The appeal to the field concept continued. "It is a rather singular fact,.... that this concept has never acquired quite the general popularity and prestige of.... (gradients and organizers) ... perhaps partly because its validity is so completely taken for granted by working embryologists, perhaps partly because no writing embryologist has yet taken the trouble to construct a single monolithic volume in which all known embryological data are subjugated to generalization in terms of fields" (Oppenheimer, 1967, p. 15) And yet a statement of the kind "the chordamesoderm area ....(is)....an equipotential field with diffuse outlines and a center of activity near the dorsal lip.... is little more than a formulation of the problem" (HH, p. 242).

Before the war, as we have seen, the concept of induction was poorly defined. "(T)he term "induction" has been stretched in more recent years by several authors to such an extent that it has no longer such distinctive meaning and has become ambiguous" (Weiss, 1935, p. 650). In so far as it was associated with chemical studies the concept helped resolve few of the issues. The frustrations met with in unsuccessful attempts to identify relevant chemical factors further eroded interest and perpetuated the aura of a failed enterprise. Chemistry was increasingly a distraction from central principles; because it concentrated attention on neural induction other possible examples of the inductive mechanism were downplayed. Despite its apparent insignificance in the research priories of most embryologists, it would be a mistake to think that induction had disappeared as a component in embryological thought. In fact, there was a steady trickle of new experimental evidence and an increasingly comprehensive list of body organs could be described as originating through classical inductive routes. (Listings of such known inductions can be found in Needham 1942, p. 290, 302-3 or Nieuwkoop *et al.,* 1985)[51]. (Fig. 9). The important point to make is that for many people induction had largely become an assumption.

There is clear evidence in Holtfreter's accounts that, in marked contrast to the situation before the war, induction was becoming differentiated from other possible pattern forming embryological mechanisms; it had now become explicitly and unambiguously defined. On the newly clarified definition reached by Holtfreter and Hamburger it is not defined by criteria set by studies of the chemistry of induction in the way Waddington's evocation/ individuation formulation had been. Now induction is defined in terms of cells, cell layers, cell masses and intercellular relations (as exemplified by a detectable concentration of interest on "epithelial-mesenchymal" relations). In 1951 Holtfreter pointed out that; "As a rule, inductions are associated with...directed cell movement, invagination, delaminations, etc..... We shall disregard these more secondary processes and focus our attention upon the "material" rather than the "dynamic" determination (Vogt, 1923) of the cells in question" (Holtfreter, 1951, p. 118). Here we can see how, even for an embryologist so deeply involved in studying cell locomotion as well as induction as Holtfreter, there was a perception that issues of cell differentiation and of patterns of cell differentiation could be categorically detached from issues of morphogenesis and movement[52]. Holtfreter's reference to Vogt shows that he is still influenced by the distinctions that Spemann had grappled with in the early 1920s. As we noted above, Waddington subscribed to exactly the same sort of categorization.

Waddington occupied a key role in the UK as the one person best placed to embrace the whole broad picture of embryology, and who could authoritatively promote general theories concerning "pattern formation". He is in many respects a truly representative figure of the position the subject had arrived at by 1968, and a link with the direction it was next about to take. Increasingly in the 1960s he continued the interests of the Theoretical Biology Club, in a series of books ("The Strategy of the Gene" (1957), "Biological Organisation, Cellular and Sub-Cellular" (1959), "New Patterns in Genetics and Development" ((1962)) and then in four IUBS Symposium volumes, "Towards a Theoretical Biology". Many of the participants of the IUBS meetings were physicists and mathematicians, and now the emphasis was to seek clarity regarding the remaining problems in biology in a formal mathematical or modeling approach. Referring to Wolpert's "beautiful analysis of early sea urchin development" Waddington remarks; "Studies of this kind are certainly the most fashionable and probably, at the present time, the most rewarding approaches to the investigation of fields. One must beware however of supposing that they are likely to provide us with more than a very general picture of the overall character of the processes going on within the field" (Waddington, 1966b, p. 117).

1.4 Positional Information

At the end of his book (H, p. 171) Hamburger quotes Wolpert as follows; *"I regard the misuse of concepts of induction as a major feature preventing progress in understanding pattern formation"* (Wolpert, 1971, p. 184)... and *"Induction and its related concepts, which have so dominated embryological thinking, have completely obscured the problems of pattern formation by emphasizing the information coming from some other tissue rather than the response in the tissue which gives rise to the pattern .... (finally speaking of)..... the failure of inductive theory to consider the problem of spatial organization"* (Wolpert, 1970, p. 202-3). Hamburger comments that; *"We have come a long way from Spemann's discovery of the head and trunk organizer in 1931 to an understanding of organizer action in terms of the gradient distribution of two inductive agents..... I hold out hope that (my) last chapter can clarify misunderstandings of the kind expressed in the.... (foregoing).... quotations".* (See also HW, 1986, p. 231). On one level these dismissive, brief statements by Wolpert are a measure of the low stock in which the classical tradition had come to be held.

Brief as Wolpert's comments on induction were, there are many clues available in the written record about the considerations that lay behind them, particularly from Wolpert's own accounts of these historical episodes (Wolpert, 1986, 1989, 1996; Lewin, 1972; Smith, 2000, from which most of the quotations in this section are taken). One thing is certain. Wolpert's comments on induction were part of the first formulation of a theory which provided an entirely fresh start to the history of approaches to understanding developmental organization. Wolpert first presented his concepts relating to positional information (hereafter PI) in Waddington's symposia on theoretical biology in 1966, 1969 and 1970 (Waddington, 1968, 1970, 1972). Additional lengthy and detailed presentations were published in 1969 and 1971. *"The basic idea of positional information is that there is a cell parameter, positional value, which is related to a cell's position in the developing system. It is as if there is a coordinate system with respect to which the cells have their position specified. The cells then interpret their positional value by differentiating in a particular way"* (Wolpert, 1989, p. 3).

Wolpert had been trained as an engineer in South Africa. Having worked initially (from about 1956) with Danielli at Kings in cell and molecular biology - working on cell membranes, fertilization, cell motility and division, mostly with sea-urchin cells - scientific visits to Sweden (c1960-5) led to collaboration with Gustafson, a student of Horstadius (leader among the Swedish gradient theorists) where his main interest was the mechanics of cell behaviour

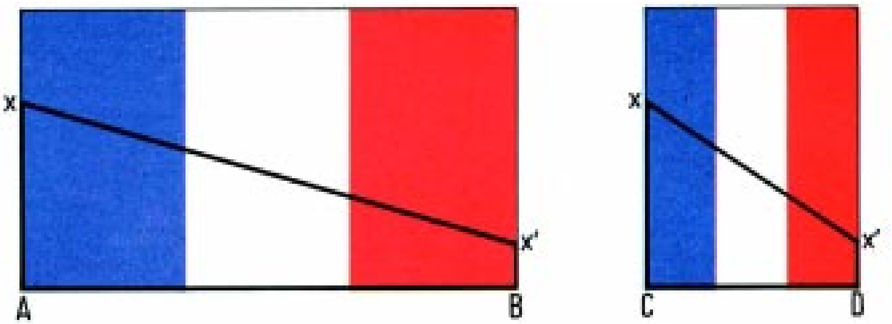

Fig. 10. The French Flag Model. *As published in Gray's Anatomy; "a line of cells .....are considered to have three possibilities for molecular differentiation - blue, white or red, and they form a correctly proportioned French Flag whatever the number of cells in the line, and even if parts of the original line are removed.... (the case shown on the right).... It is assumed that each cell is assigned a positional value by appropriate signals with respect to reference sources at the ends of the line" (Reprinted from: "Gray's Anatomy", 36th edition, Eds. Williams, P.L. and Warwick, R., p.87, 1980, by permission of the publisher Churchill Livingstone).*

involved in sea-urchin gastrulation[26]. Wolpert's papers on the subject demonstrate a modeling approach and his search for explanations of coordinated cell movements based on a few simple, modular principles of cell adhesive behaviour. He says (Wolpert, 1989, p. 12); *"From the beginning I had great difficulty with gradient theory and how it could explain patterning and size regulation".* From around 1964 he worked on Hydra regeneration with Webster; a "simple regulating system to work on pattern formation" (Wolpert, 1989, p. 12) - it was also a "winter animal" (S, p. 87), i.e. available throughout the year. *"I was trying to understand regeneration, but I think I had invented the French flag problem already, because I knew about sea urchins and Hydra seemed rather like sea urchins"* (S, p. 87). He arrived at the PI theory in two distinct stages (Wolpert, 1986, p. 357-8). As the result of extensive theoretical considerations (working especially with Michael Apter (e.g. Apter and Wolpert, 1965), "a psychologist with an interest in computers" (Wolpert, 1989, p. 12) and author of *"Cybernetics and Development"* (1966)), Wolpert first formulated the central problem of developmental pattern formation as he saw it. He presented this first at the symposium in 1966 in the form of the "French Flag Problem" (Wolpert, 1968) (Fig. 10). In this model he is concerned to explain how discrete patterns of regional differentiation can emerge in an embryonic system that displays the properties of regulation; in fact Wolpert initially focused on the specific manifestation of regulation of "size invariance", which is well demonstrated by *Hydra* and sea-urchin and in regenerating systems (S, p. 87). Having pointed out the problems with previous models (i.e. gradient models, and particularly those of Spiegelman and Rose) he concludes that any gradient-based model must include the additional parameters of thresholds and polarity. (What he meant by "polarity" is sometimes unclear (as he seemed later to acknowledge when he reviewed the history of the term, Wolpert, 1986, 1991)). "Thresholds" are needed in order to define regions of discrete differentiation and "polarity" is needed to define where (and in what direction from a dominant gradient "source") those regions come to lie. Together these two parameters were seen as essential to allow cells to adopt organized and discrete states within the initially uniform array of as yet un-determined cells.

It was a short distance from this formulation of the problem to the concept of positional information itself, presented at the third symposium in 1968. Wolpert's sole explicit argument against "induction" is to point out (Wolpert, 1970, p. 202-3) - referring to Schotté's experiments (EDI, Chapter 17) - how non-specific inductors seem to be and how the role of the responding cells has been neglected. Referring to the universality and simplicity of the DNA code, Wolpert clearly hopes and expects that the rules of embryology will prove to be equally general across species. *"For me, the most significant contributions to the study of pattern formation over the last thirty years come from the work of Stern on genetic mosaics and the concept of prepattern......(they have)... shown that there is complete autonomy of cell differentiation in mosaics of different genotypes.... (in* Drosophila*)... Contiguous areas of different genotypes form their appropriate phenotypes almost regardless of the nature of the neighbouring cells"* (Wolpert, 1970, p. 220). This evidence illustrated for Wolpert the "universality" of the position-defining mechanism across different organ rudiments in *Drosophila* - that is "universality" within the single embryo; Schotté's data showed universality across species - as well as the way that cell responsiveness alone determines final differentiation. Although the transition from "problem-definition" to "solution" appears to have occurred rather suddenly in 1968, there are clear hints much earlier (e.g. Gustafson and Wolpert, 1961, last paragraph) of similar patterns of thought.

In his 1986 survey Wolpert is particularly concerned to "consider why the link between gradients and that of positional information took so long to establish" (Wolpert, 1986, p. 347). On first appearance this is a surprising statement. Afterall the French Flag Problem was presented in the form of a gradient model from the start. Although Wolpert has often pointed out that PI could in principle be established by other mechanisms, gradients have throughout been used as the best available evidence for PI in practice. In Wolpert's recollection "gradients had become very unfashionable" (Wolpert, 1989, p. 12). He recalls that the Swedish tradition (centred on Horstadius and itself much influenced by Child) of gradient models to explain sea-urchin development was not a significant influence on him. Working as he was on *Hydra* he was well aware of the influence of Child's concept of gradients. In part his initial apparent reluctance to embrace gradients may well have arisen because he assumed that to accept gradients was to accept Child. The need to detach gradients from Child's perspective is suggested in the following quotation; *"... the paradigm up to the 1950s which dominated thinking about gradients was that of energy metabolism.... (i.e. Child's theory).... Only when the paradigm shifted to information transfer in biochemistry, with the coding problem in relation to DNA and protein clearly defined, did the concept of positional information emerge"* (Wolpert, 1986, p. 347). *"(P)ositional information as here defined has features in common with the double gradient theory of Dalcq.... It should be emphasized that the ideas that a cell's position is important in development is not a new one, but has been explicit and implicit in the writing of various authors at various times"* (Wolpert, 1970, p. 202). Thus, it seems likely that Wolpert had initial reservations about gradients, but that a recognition of the peculiarities of Child's use of the concept allowed him to distinguish the general idea from that specific version.

How was Wolpert's theory received? The earliest comments came from Waddington himself; *"I should like to mention some phenomena which seem to me relevant and in some cases not very easy to assimilate into Wolpert's scheme.... Stern's studies on "prepatterns" are, of course, interpretable very easily in terms of Wolpert's theory, but they do not, in my opinion, provide any noticeable support for it"* (Waddington, 1970, p. 233). (Waddington had already made critical comments on the *Hydra* work; *"Many other aspects of the field activity have been omitted... (and) ...are defined only operationally, and it is by no means clear how they should be interpreted in chemical terms"* (Waddington, 1966, p. 121)). Soon after, one of Waddington's colleagues described the situation as follows; *"In the last few years Wolpert (1971) and Goodwin (1971) have developed theories attempting to account for the control of axial differentiation. Neither of these theories is as yet supported by enough experimental evidence for it to be acceptable, but they have aroused much interest.....The reader will see that there are still many flaws and unproven points in these arguments, and many more experiments need to be devised to test Wolpert's theory"* (Deuchar, 1975, p. 111). *"To support Wolpert's ideas, more observations are needed on the extent to which cells in embryos receive information about their relative positions, during axis formation"* (p. 114). Another Waddington associate wrote; *"There are a number of difficulties in the way of accepting positional information theory, at any rate as a universal mechanism: the separation of a special process of information signalling from a second process of interpretation and implementation; the necessity for a special and quite unknown mechanism for setting up special groups of cells as boundaries; the burden of complexity which is placed on the interpretive mechanism as a price for simplicity in the signalling system"* (Ede, 1978, p. 149). Oppenheimer commented that; *"Because most attempts have been unproductive, Wolpert's efforts to discover how a cell knows its place in its cellular surroundings are welcome"* (Willier and Oppenheimer, 1974, p. xv). *"Even if ... aspects of his thought are not new, his approach is fresh, and may engender interest in the study of overall pattern in development"* (p. xv-xvi). The theory received a significant endorsement in 1970 when Crick (1970) argued on theoretical grounds that a diffusion model of embryogenesis was entirely plausible.

Around 1970, after a brief interest in amphibian limb regeneration and insect cuticle, Wolpert - in a switch from invertebrates and regeneration to embryology in a vertebrate system - adopted the chick limb bud as his main research object and this has remained the principal test-bed for his theory ever since. A number of the early commentaries on the PI model came from embryologists working on the chick limb bud, notably Saunders; *"Prominent among efforts to develop a satisfactory working model.... (that is)... "formal models that seek to establish conceptual frameworks within which development and regeneration of spatial patterns may be discussed.... .are those of Wolpert and his students"* (Saunders, 1982, p. 490).... *"The foregoing model.... (PI applied to the limb)... has stimulated a good deal of experimental work. Many of the results are highly compatible with it. ....Other evidence, however, is difficult to reconcile with it... (referring to results by Kieny).... With respect to the ZPA as a source of a morphogen that determines positional value, the situation is now quite confusing.... Unfortunately, the idea that a morphogen diffusing from the ZPA determines positional values with respect to the anteroposterior axis of the limb has proved so attractive ....that few investigators have tried to design experiments that give a critical test of the thesis"* (p. 509).

By the time of the last Theoretical Biology symposium what Waddington calls an "argument" (Waddington, 1972, p. 286) suggests some strain; and again Waddington is critical; *"I can see the logical attraction of Wolpert's idea that one can account for pattern formation by generating a system of specifying positional information and the codebook for interpreting it, and that therefore "one never has to generate a pattern". But I think Lewis is much too facile about how the cells "have merely to interpret" their positional information"* (p. 145). Wolpert has referred several times to the less than welcoming response he received in the USA at the time ("Ed Zwilling ..turned his back on me" (S, p. 88)). In 1976, I (Horder, 1976) specifically reviewed PI in relation to the evidence for induction. I argued that the two theories were fundamentally at odds and that a comprehensive theory could be quite adequately built on the basis of induction.

Commentary: A number of influences are apparent in Wolpert's first presentation of his model. There is the new information-based view of biology emerging from understanding DNA coding, which is contrasted with and preferred to the "metabolic" view of gradients promoted by Child. (The very word "information" figures in Wolpert's new terminology. "Information theory" was then popular in psychology). Spiegelman was at that time linking the newest results from molecular biology into models of development (Gilbert, 1996); Waddington had been doing so for some time. Wolpert refers to "a desire for universality and how to get from the genes to pattern" (Wolpert, 1989, p. 12) and his "envy of the molecular biologists having general principles" (S, p. 87). Fellow South-African Sydney Brenner was an early support. Wolpert was influenced by Goodwin (at that time working closely with Waddington) and he contrasts his own interest in spatial organization with Goodwin's focus on "temporal organization" as a model for development (e.g. Turing standing waves, the "phase shift" model). His initial interests were invertebrates and regeneration; hence the influence of Child upon him. The concern with both regeneration and model building remain priorities for him even today (as is made clear in Smith, 2000).

As he says of himself, some of Wolpert's thinking was "sort of in the Waddington tradition" (S, p. 88). Waddington's influence is evident on many levels. He tacitly lent Wolpert his support by offering him repeated access to his symposia and publications, not to speak of access to a receptive audience (which included Thom, Maynard Smith, Goodwin, Kauffman) with a collective approach to biology and methodology that chimed exactly with Wolpert's position. The formalism of the terms within which PI is presented (including such concepts as "polarity", "interpretation", "positional value", "universality" and "nonequivalence" which have since been variously dropped) would certainly have appealed to his listeners, and would have given the theory an apparent, almost quantitative, precision that they probably regarded as sadly missing in embryology hitherto. An important aspect of Wolpert's approach to research is that he regards himself as a theoretician, rather than an experimentalist. (S, p. 88). The PI model was not based on any new empirical evidence; Wolpert often refers to Waddington's texts as sources for the already published evidence he deploys. There is one further interesting link between Waddington and Wolpert. From the start Wolpert seems to adopt Waddington's three-way division of the phenomena of development into differentiation, pattern formation and morphogenesis. Thus in the opening of his 1971 review he says; "A useful....distinction between form and pattern (cf. Waddington, 1962), is that form involves cell movement and changes in shape, its genesis requiring an understanding of the forces involved, whereas pattern does not involve changes in shape or cell movement but rather the specification of spatial difference" (Wolpert, 1971, p. 184). In Wolpert's model cell differentiation is a matter for positional interpretation; patterning is controlled by the quite separate parameter of the positional information morphogen. Morphogenesis is an entirely distinct issue and of noticeably less interest (despite, and perhaps because of, the morphogenetic theme of his sea-urchin work, now entirely left behind).

Although Wolpert also uses the word "field", gradients are central to his thinking and were a feature even in the first PI papers. Their importance is evident in the way gradients (as "diffusible morphogens") are invoked as the best "evidence for" positional information (e.g., *bicoid* in *Drosophila* and retinoic acid in the chick limb, in Wolpert, 1989). "There is now substantial evidence that gradients in positional information underlie pattern formation in a variety of organisms" (Wolpert, 1978, p. 133-4). More importantly the gradient is the essential (and only) operational feature defining the model; that is it defines the way in which the model explains integrated pattern formation and regulation. Wolpert's treatments of PI regularly deal in detail with the position-defining mechanism (i.e. the gradient); in contrast, while he acknowledges the crucial importance of the mechanism of interpretation of PI, " (u)nfortunately, very little if anything is known about it" (Wolpert, 1971, p. 211). "The interpretation of positional information is the key process in the formation of pattern and is the *raison d'être* for positional fields. ...Unfortunately very little if anything is known about it" (Wolpert in Waddington, 1972, p. 91).

1.5 Up to the present

A few very brief remarks are relevant concerning events in the period after the introduction of positional information. Slack (1999) provides an entertaining and sometimes revealing eye-witness account of recent trends in developmental biology. Gehring (1998) offers an alternative, molecular genetic perspective on the recent history. Since 1968 the discipline has taken on the appearance of much activity and great change. Today it is a rare developmental paper indeed that does not involve techniques derived from molecular biology. The overwhelming impression is that the subject has been successfully subsumed within the molecular revolution in biology.

As predicted in Horder and Weindling (1986) the organizer and induction have now been "re-discovered". The organizer, in the frog, chicken and mammal, has once again become a subject of considerable research interest (e.g. see Harland and Gerhart, 1997; Tam and Behringer, 1997), but not in the earlier sense in which the focus was neural induction. The emphasis now is on the detailed dissection of the molecular constitution of the organizer region itself. Now it is commonly referred to as "Spemann's organizer", to distinguish it from "organizer regions" operating elsewhere in the embryo (see Wolpert *et al.,* 1998). Gurdon was the author of a leading review on induction in 1987: in another (1998) review he places gradients centre-stage and ends by summarising Wolpert's theory. In Wolpert's recent textbook (Wolpert *et al.,* 1998) induction is covered alongside positional information.

In recent developmental biology gradients (now often called "morphogens") have come to occupy a prominent place. *"Developmental biologists have been almost obsessed by the idea of morphogens, substances that when presented at different concentrations elicit different fates in a responding tissue"* (Harland and Gerhart, 1997, p. 631). A much favoured research model, triggered by Nieuwkoop, is the *Xenopus* "animal cap" assay; this maximally simplified, *in vitro* technique is ideal for studying molecular interactions underlying mesodermal induction while entirely avoiding questions of morphogenesis or tissue organization as such. *Drosophila*, despite its specialized (and invertebrate) features, is widely regarded as having provided the paradigm example of a morphogenetic gradient (*bicoid)* (Gehring, 1998). Wolpert has been part of a considerable concentration of interest on the chick limb; it could indeed be said that the limb-bud has been the principal model experimental system for exploring, exemplifying and testing PI. (Thus *sonic hedgehog* is widely accepted as the molecular basis of the ZPA (zone of polarizing activity) in the chick limb alongside gradients (retinoic acid or otherwise) as controllers of limb pattern). The key issue throughout is identifying the gradient conveying PI rather than "interpretation"; "There are many details relating to pattern formation involving positional information that remain to be worked out. The most notable relates to interpretation" (Wolpert, 1996, p. 363). *" I think the interesting thing at the moment is how you set up and interpret gradients. This is a really open and exciting question"* (S, p. 88). *" (A)fter all that effort it's still not clear how sonic specifies position in the limb"* (S, p. 89).

The phrase "positional information" is now deeply embedded within the common vocabulary of developmental biologists. It is used frequently and unquestioningly; it is rarely explicitly attributed to Wolpert or his model. PI is presented in current textbooks including such standard ones as *"The Molecular Biology of the Cell"* (Alberts *et al.*) and Gray's *"Anatomy"* (Fig. 10). The term is now, one suspects, sometimes used in a loose and general sense, not to imply any model at all, but merely to refer to the "problem of development" itself, i.e. how cells know how to become different.

Commentary It is, of course, impossible to say how much Wolpert has influenced the direction taken by developmental biology. But there can be little doubt that he helped significantly to set the preconditions that allowed present molecular trends to flow naturally. Afterall Wolpert's model provides an almost tailor-made framework within which molecular observations (whether they concern gradients, or genetic factors (e.g. homeotic genes) thought to be switched selectively by gradients) can be related to the supposed mechanisms of embryogenesis. "Lewis Wolpert is one of the most influential developmental biologists in Britain and the world" (S, p. 85). "His concept of positional information....changed the way we think about pattern formation in the embryo and allowed new generations of molecular developmental biologists to frame their questions in a way that would give sensible answers" (S, p. 85).

SECTION 2

We have now reached the point when I can bring together the underlying objectives of this paper. I now address the question of how the two, above described, dominant embryological perspectives relate to one another in scientific terms and how historical forces have contributed to the transition between them.

2.1 The scientific dimension: problems and puzzles

Standing back from the chronological account of events, we return to the fundamental dilemma briefly raised in the Introduction; exactly how, in scientific terms, are the concepts of the organizer and of positional information related?

I argued in 1976 (Horder, 1976) that the concepts of induction and PI are at root opposed to one another. Wolpert's model rejects the very possibility of induction in the following way. The positional information model relies on long-distance communication across the embryo (i.e. in the operation by the position-defining parameter) and autonomy of cell expression ("interpretation" of positional value). In the original, basic form of the model, pattern formation requires simply that cells independently read off their positions from an overall concentration gradient of a PI "morphogen". This is essentially a "two-step" (Wolpert in: Waddington, 1972, p. 86) process - of setting up PI and then of reading it out. "(T)here is no interaction in a field between parts of the pattern as distinct parts" (Wolpert, 1971, p. 191). Induction, on the other hand, specifically demonstrates that cells are dependent in their differentiation on their immediate (usually juxtaposing) neighbours - that is, there *is* interaction between parts and communication is short-distance - and also requires that pattern formation is a sequential and multi-stage process (an "epigenetic cascade"). In a later review Wolpert (1989, Table 2) confirms, in rather similar terms, the contrasts inherent in the two viewpoints.

In my earlier reviews pointing out the fundamental distinction between the two accounts (Horder, 1976, 1983, 1993) my primary aim was to show that, despite perceptions at the time, induction was more than adequately supported by the experimental evidence and that it was a sufficient basis on which to explain embryogenesis, while also inter-relating with the whole range of available experimental and descriptive data more satisfactorily than PI. (I systematically discussed all experimental examples selectively given as supporting evidence by Wolpert to show how they were open to explanations within an induction-based framework). A key element of my presentations was to show how cell movement is an integral part of the process by which induction mediates orderly pattern formation. *"(T)he locations at which a given cell type is formed, and indeed whether it is formed at all, is a direct reflexion of the morphogenetic events that bring about confrontations.... (between uncommitted cells and the appropriate inductor)"* (Horder,1976, p. 184). Gastrulation movements are, for example, essential pre-requisites for the positioning of the neural inductors, evagination of the eye rudiment towards the surface ectoderm is an intrinsic part of the process of lens induction and so on: the examples are too numerous to list. (The organizer can now be seen as merely a first morphogenetic step in the epigenetic cascade[53]). On this basis I also showed how one could arrive at explanations for the whole range of phenomena met with in developing systems, covering the wide variety of organ systems in which induction is well documented, including their gradient features and their all-important regulative properties[51]. The missing element in existing approaches to the analysis of developing systems in terms of fields - in which the limb has been the classic case - has been a careful consideration of what underlies their "self-organization" (we lack any better word to refer to this defining feature of fields). Gradient properties, fields and self-organization can, and must, reflect the various forms of mechanical interactions that occur in developing tissues; I argued that the morphogenetic processes within cell populations can in themselves explain and play an essential mediating role in generating just these kinds of embryological properties and phenomena. The potentially crucial involvement of morphogenetic tissue behaviour in the regulative delimiting and structuring of organ rudiments is most easily demonstrated in cell sheets, i.e. in such features as folding, rounding up, invagination, outgrowth, branching, cavitation, shaping, etc. Neural tube formation, eye evagination, gastrulation and somitogenesis, formation of kidney tubules, the limb apical ectodermal ridge are examples. Less obvious is the role of such processes in the mesoderm (of which the limb-bud mainly consists), but cell aggregation prior to cartilage formation is a morphogenetic process of evident importance. Hinchliffe and Horder (1993) reviewed the case of the limb and argued (using known examples of local tissue interactions, involving the full range of cell types involved in limb formation) that the development of the limb must be viewed as an epigenetic cascade; rather than being laid down directly by any overall position-defining or field-like mechanism, its patterning is the indirect outcome of multiple types of short-distance interactions - inductions, movement and mechanical ordering of cells among them - operating multiplicatively in space and time[51].

I highlighted morphogenetic movements because they are an essential (though hitherto largely ignored) linking factor, which explains how inductive events are located and deployed in space and time in order to make integrated pattern elaboration possible. But I also used them to stand for the whole diverse class of "epigenetic cell interactions". Being so diverse, examples are difficult to survey, classify or cover systematically, but include (in addition to induction and cell movement) cell death, growth control and the many effects of "function" and functional demand on tissue structure (Horder, 1983). As *the* classic example of an epigenetic, short-range, cell-to-cell interaction, induction remains the most obvious of many such phenomena not accounted for within the PI model. It might be thought that the status of induction as a valid developmental mechanism is open to doubt on the grounds that it still cannot be characterized in definitive chemical or molecular biological terms. But this is to assume, as so often happens in today's molecularly-driven thinking, that such a definition is strictly necessary. The classical evidence shows, on the contrary, that it is sufficient to define induction in purely operational terms, i.e. as neighbourhood cell-to-cell dependencies leading to particular forms of differentiation in the responding cells. Given that embryogenesis is a vastly complex and multifactorial matter, then complex explanations are inevitably required, and levels of explanation above the molecular fundamentals are valid and necessary[53,54].

Morphogenetic cell movements are, of course, an ubiquitous and highly characteristic feature throughout developing systems. (They are also "inevitable" in the sense that any cell necessarily, among its many roles, cannot avoid having mechanical effects in a tissue). PI fails notably to take account of, or explain the role of, cell movements; such movement in itself would create problems in the establishing of, and the maintenance of spatial stability within, any supposed position-defining mechanism. In so far as Wolpert might, with his emphasis on gradients, be seen as having led developmental biology back to positions akin to those of Driesch and Child, the arguments repeatedly raised against all gradient-field models presumably still apply. Spemann discussed them in some detail. With or without gradients, the concept of positional information has much the same operational properties as gradients and fields. Unless other considerations are added on, all three theories (fields, gradients and PI) treat development essentially as a mechanistically single-dimensional process linking the initial conditions in one step to the final adult pattern of morphology. All three share the difficulties of accounting for the way in which sub-fields come to be defined within the initial, single, overall embryo field. How are their new sub-boundaries specified? This is a particular difficulty for PI because Wolpert claims that exactly the same ("universal") position-defining gradient operates for each sub-field as well as defining the earliest overall field of the embryo.

Conclusions

I conclude that the two modes of explanation are comparable in the sense that they offer alternative accounts of the same general problem of the control of pattern formation. Both are capable of broad coverage of the phenomena most in need of explanation. Therefore PI can be said to have taken the place earlier occupied by the organizer. The points that I raised in 1976 apply unchanged today; the difference of approach is quite fundamental (for example, as regards the implications about the cell properties required). It is of course possible to seek to link or reconcile the two approaches, but there is little point; to do so would gradually erode the defining tenets of the PI model. The differences suggest widely differing background sets of assumptions about embryos and cells. Where did PI come from and why? How much did Wolpert owe to past concepts? Was PI as novel as it might have seemed to be?

2.2 The historical dimension: some factors and possible explanations

It is surely quite remarkable that a body of data and experiment built up over a 50 year period and as well founded as that pointing towards a concept of induced-based epigenetic cascades should have been so fundamentally overturned in the 1960s. This is all the more remarkable when its replacement covers so much less of the range of available evidence requiring explanation. The forces needed to explain this process of conceptual change must be potent ones. It is surprising too to find in Wolpert's early papers on PI that there is so very little discussion of the concept of induction. Wolpert's comments, as quoted above (p. 114), are virtually all he has to say; certainly there is no systematic survey or critique of the relevant experimental evidence. (No such survey appears in his subsequent writings at any point; even Table 2 in his 1989 paper lacks supporting references or discussion). On the other hand Wolpert's brief comments do offer some clues as to the circumstances that may underlie the transition to PI. They imply - referring, for example, to "the failure of inductive theory to consider the problem of spatial organization" - that from his perspective at the time the inductive tradition had failed comprehensively, and to such an extent that it no longer needed to be taken into account. In seeking explanations we need therefore to consider two aspects; what perceptions about Spemann's legacy had built up at the time Wolpert introduced his model, and, secondly, what are the origins of Wolpert's new model as such?

In what follows I summarise and interpret points arising from the foregoing historical account, with a view to listing factors and possible causes that offer explanations. A potentially endless number of historical factors could be picked out; my selection is, needless to say, a matter of interpretation. In accounting for the movement of events during the time period under consideration, some contributing factors must count as "incidental"; the effects of war or career paths, access to new techniques, choice of organisms, and so on. Inertia played its part - the result of general lack of interest in the issues especially when, at certain periods, embryology was not a popular research subject - and we must consider the possibility of frank intellectual confusion at times. I concentrate as much as possible on the origins of the scientific issues themselves, and I will therefore not consider the many possible extra-scientific factors which contribute to the dynamics of conceptual change, i.e. all the contextual forces (personal, motivational, social, political, national and so on) already so well explored by Hull, 1988, Harwood, 1993, Kevles, 1998 and Jardine, 2000 for other biological areas.

(i) Shifts in Spemann's legacy. Why did induction fail as a recognised basis for epigenesis?

(a) *Persistent and accumulating difficulties within Spemann's scientific programme*

I start by listing general themes arising directly out of Spemann's scientific contribution that increasingly created difficulties over the time period leading up to Wolpert's model. I am here abstracting from my earlier account; quotations included there provide direct evidence regarding perceptions at the time;

- terminological and conceptual confusions (i.e. obscurity of distinctions between organizer, induction, fields, gradients, self-organization; also between competence, *Bahnung,* labile determination, etc, and the respective roles of responding tissue and inductive stimulus). The terminological overlapping and imprecision suggested a lack of clarity in underlying concepts.
- mystique of the "organizer" concept; the early promise and renown of the concept contrasted awkwardly with suspicions about its imprecision, obscurantism and even vacuousness. The concept was at the start only "preliminary" (EDI p. 368), and its meaning and definition became no clearer as more became known about embryological phenomena and as "fields" were invoked.
- overt expressions of unease in the literature; the organizer concept was repeatedly subject to explicit or implied criticism, notably suggesting that exaggerated claims had been made for the concept. These built up especially among those immediate successors who now carried Spemann's mantle, such as Holtfreter and Hamburger. Hamburger spoke of an "error" which might have contributed to the forming of the original concept. In 1988 Hamburger still lists numerous problems (H. p. 87-89). Holtfreter (as perhaps the main mediator of the Spemann tradition in the post-war period) failed to offer any coherent defense or advance.
- the concept of induction (as distinct from the organizer) was itself perceived to be insecurely established; especially as the result of the complications arising in the classic case of lens induction, the failure of the chemical approach to induction, the increasing emphasis on "self-organization" of the responding tissue, and its general overshadowing by the organizer concept. The increasing focus of induction research on specific model systems (i.e. single organs in isolated conditions, especially neural induction) resulted in detachment from their real context, and increased neglect of the "whole embryo".

(b) *The background of changing attitudes to scientific method and practice*

A potentially powerful, though often unnoticed and undefined, determinant of scientific thinking at any one time is the prevailing "methodological ethos", i.e. the "terms of reference" in which it is assumed explanations will be found for the outstanding scientific problems as perceived at the given time. Shifting assumptions about "method" often directly dictate and delimit the options - the forms of questions posed and the possible answers - in a particular scientific era. (Hull, 1988, p. 73, 297; Harwood, 1993; Keller, 1995 and Jardine, 2000 discuss the role of research style and methodological assumptions as influences in the historical development of various areas within biology). Because of the long time span we are considering here, the subject of embryology has been affected by a number of changing emphases, philosophies or fashions (Oppenheimer, 1955, p. 21-2); in any one period the focus was on a single "dominant" concept or theme which in turn determined the setting of priorities in research directions - and this, necessarily, implies that alternative possible perspectives become relatively ignored. Waddington, for example, comments on the "metaphysical attitude" impinging in the 1930s and particularly on the strong influence of Whitehead (Waddington, 1969, p. 72-81). Physics served as a model; it did so also for Spemann and many other embryologists. It was often left uncertain how much concepts taken over by biologists from other disciplines like physics were meant to be taken literally, or as analogies, models, metaphors or just images. "Machine-theory" and the "psychic analogy" undoubtedly identified for Spemann two crucial positions which influenced the direction of his research. Particularly important in the history of embryology has been the disposition of individuals towards or away from vitalism (Needham,1929; Woodger, 1929; Hein, 1972). The same polarization of attitudes carried over later into the alternatives offered by reductionism as against organicism; this is a dichotomy that it is impossible to avoid in embryology and responses to it reflect motivations and directly affect choices in research objectives.

The constant close connection between embryology and "theoretical biology" is an indication of the centrality of "concepts" and the theoretical side of the subject. (Embryologists often figured as leaders within the discipline of theoretical biology, e.g. from Roux, Driesch, Uexküll or Schaxel up to Woodger, Weiss or Bertalanffy). Attitudes to "theory" have also changed during our period; one only has to compare the approach in the "Theoretical Biology Club" before the war with Waddington's Symposia in the 1960s to see how the theoretical side of the subject has been affected by the prevailing ethos in science generally. Before the war theoreticians were concerned with "the traditional muddle of our concepts" (Weiss, 1950, p. 177). But by the 1960s solutions were sought in the form of quite specific "models", often based on specialized techniques borrowed from the physical sciences. As my historical account shows, embryology has suffered repeated confusions due simply to imprecisely defined terminology or lack of clarity in fundamental distinctions. Questions of concept formation and differentiation of terminology have been of equal importance to changes in laboratory methods (Woodger, 1948). *"It is an unfortunate fact that the basic terminology of developmental biology has been in a state of considerable confusion throughout the whole of the modern period of about the last forty years, particularly in connection with processes of the kind to which one might apply the field concept"* (Waddington, 1966b, p. 105). Looking at the work of Spemann or Wolpert it is clear that their experimental research programmes were largely dictated by their theoretical models. Throughout the 1920-30s Spemann's experiments had the underlying objective of dissecting the organizer region with a view to unravelling its precise mode of action. Wolpert's work on the chick limb has been explicitly framed with the aim of exemplification and exploration of positional information. Embryology seems to be particularly dependent on its central concepts (Oppenheimer; 1955, p. 25-26, 36-7); not just to guide choice of experiments and research priorities but in the broader sense of providing an explanatory and integrating framework without which the complexity of relevant data about embryos would be overwhelming, meaningless and unmanageable.

Reductionist trends affecting biology in general have been a prevailing influence which has affected embryology massively. Reduction was the intention behind *Entwicklungsmechanik* and we have noted the effects of what gradually followed it; first biochemistry (chemical identification of inductive stimuli), then cell and eventually molecular biology, and molecular genetics. There has been an inexorable trend through the period towards "methods" that aim at a "solution" based on the identification of specific causal agents. Clearly all of this eventually narrows the "types of explanation" that are considered and are regarded as acceptable within the field of embryology, and increasingly integration - the consideration of the whole embryo - tends to be discounted as a result. From the 1970s identification of causes in terms of DNA sequences would increasingly become the hoped-for ultimate objective (see Keller, 1995; Gehring, 1998)[54]. Alternatives, such as organicism, are rarely discussed any more by scientists. Terms like "the organizer" and "positional information" (and even more so, "field" and "morphogen gradient") create the impression that they signify single, well-defined causal mechanisms, potentially amenable to direct and substantive identification in physico-chemical terms. The failure to identify the chemical basis of induction was all the more damaging as reductionist expectations and criteria of success increased. In this light Spemann's organicism, his reference to germ layers rather than cells, and his perceived resistence to, or lack of interest in, genetics, the reductionist strategy and the chemistry of induction intensify the questioning of his work as it comes to be seen from the modern perspective.

(c) *"Myth" creation*

The way a scientific figure (or, indeed, a concept like the organizer) comes to be perceived in retrospect can be affected by a further effect of the historical process which adds an entirely new, extra dimension to what has already been discussed. I will call this process "myth creation" (Kragh, 1987; Hull, 1988, p. 18-19; 372-5; Horder, 1998). There can be little doubt that Spemann became increasingly suspect for many post-war embryologists on the grounds that he was a "vitalist", an inference encouraged by the obscurities of certain passages in his writings, such as the last paragraph of his book. The imputation was reiterated throughout the post-war period and discussed in print by people who presumably were fully aware of the implications and of the crucial difference between "vitalism" and "organicism" (see Bautzmann, 1950, 1955; Goodfield, 1969; Hamburger, 1969, 1988, 1999; Maienschein, 1997, p. 226 (refers to "Spemann's vitalism") - later Hamburger (1988, p. 67) apparently seeks to moderate any such description; Fässler (1997) also tries to maintain a neutral position). Carefully considered or not - and regardless of how closely Spemann can be considered to have approached a vitalistic position - the mere use of the word is loaded, and increasingly so as the vitalistic position has become more and more untenable. Any such accusation aimed at Spemann necessarily invites immediate comparison with Driesch: his open vitalism was notorious and eventually an object of ridicule. But the important point is that, once created, myths like this tend to persist. As part of the general tendency over time that applies to all scientific beliefs, as they are handed down from generation to generation, such myths become simplified, exaggerated and increasingly detached from any original, relevant evidence. A point is reached at which it does not matter whether the myth is true or how much it is true or what it is based on; it is only the message that is handed down that eventually matters. The organizer concept has shared in this mythologisation.

Conclusions

Wolpert's approach to induction is likely to have been a fair reflexion of the general position, at least among British embryologists[55]. In the period prior to Wolpert's model less and less actual research was addressed to the topic of either the organizer or induction.

Spemann's legacy had largely become a matter of textbook accounts and the organizer, in so far as it did survive, stood symbolically for the entire tradition. (In textbook accounts it was hard to separate out induction from the organizer. In several early papers Wolpert speaks as if "the organizer" is the prime representative finding, synoptic of the whole body of work). By the time Wolpert proposed his model, the "classical" tradition within which induction was embedded was increasingly being remembered as a body of evidence and propositions dogged by persistent doubts and criticisms; unresolved, inadequate, confused, suspect and out-dated. "There has been almost no major advance on these ideas... (the concepts of induction ..elaborated in the 1920s and 1930s) ...since then" (Wolpert,1970, p. 200) As a live, active scientific subject induction had faded from the perspectives of the average working embryologist, and even among those who still "assumed" that it was part of the array of developmental mechanisms.

A significant factor in the way Spemann's reputation has been created is the relative inaccessibility of relevant literature for English-language readers. Only two of his papers were in English (the 1924 paper was only translated much later). The textbook of 1938 suffers from all the difficulties of translation, and the German original was itself a "demanding" book, lacking an index. And yet Spemann's book stands as a uniquely complete treatment of all the pre-war work. Indeed there is no other source that approaches it in the way it reviews the original evidence in full detail. With the passage of time its inaccessibility to modern readers has only increased, to the point, as we have seen, that many sections are only interpretable with extreme difficulty.

Perhaps the most damaging effect of the simple passage of time was, inevitably, that among younger embryologists Spemann's work would not just be neglected, but that it would effectively have been forgotten as a still potentially relevant body of scientific work. The details of the evidence and arguments contained in Spemann's work became unfamiliar to modern workers. There is no more remarkable evidence of the changes that had occurred in Spemann's legacy than Jacobson's work (Jacobson, 1982); reflecting a basic questioning of the reasoning that led up to the discovery of the organizer, Jacobson not only thought it necessary and worthwhile to repeat the experiment; he misinterpreted the result just as Spemann had initially done in 1916.

(ii) Why did the Positional Information model emerge in the form it did?

Turning now to factors that go to explain the particular form of Wolpert's model, I again summarize points that have come out of my earlier historical account;

(a) *Factors due to the general biological context of the times*

A number of the features of Wolpert's model are in tune with, and presumably reflect the direct influence of, trends current in biology generally at the time, particularly reductionist ones;

- the aspiration to the ideal represented by the discovery of the DNA code and to the new perspectives of molecular biology; i.e. the aim towards a few, simple principles of wide biological applicability. Evidence was sought specifically for "universality" of mechanisms across species.
- an emphasis on mechanisms available within the single cell; in the notion of "positional interpretation" the onus for patterned development is placed almost entirely within the single cell. The emphasis on genetics is closely related.
- the gradient concept suggests the immediate possibility of chemical identification; this does not so obviously apply to the otherwise comparable field concept.

(b) *Methodology*

With his background as an engineer Wolpert's preferred "methods" are easily understood; i.e. theory rather than experiment, emphasis on model building, the ideal of a fully definable, precise (preferably mathematical) account of the biological phenomena.

(c) *Specific background to the model*

- the PI model reflects the particular research background that Wolpert himself had come from, i.e. the study of regeneration and of invertebrates. Wolpert then saw the "problem of development" in very general (and abstract) terms. His perspective was comparable to Driesch's; he frequently refers to Driesch as one of his precursors.
- the central role given to gradients in Wolpert's presentation can potentially be traced back to a number of the early influences to which his biological apprenticeship exposed him, all of them with long histories of their own.
- Wolpert's debt to Waddington is difficult to assess, but is suggested at several points. Most specifically demonstrable is the way he consistently referred to Waddington's textbooks as his primary source on matters embryological in his earlier theoretical writings. Of particular interest is Wolpert's adoption of Waddington's three-way classification of developmental phenomena because this relates in a direct way to Wolpert's separation of the gradient mechanism from the interpretative mechanism and to his lack of interest in morphogenesis within the scheme. Waddington's categorizations can be traced back to his own earliest work[46, 49].

Conclusions

These features go a long way to explaining the content of the new model and its "terms of reference". Some of these factors are relatively specific to Lewis Wolpert himself. But Wolpert's approach was also representative of his times and this is particularly demonstrated by the fact that his model was, as we have noted, rapidly noticed and broadly welcomed by the community of embryologists when it was first presented. Wolpert's scheme evidently appeared to them to be a "new" concept (a new terminology was being offered, together with the attractions of the promise of universality and simplicity; the approach was couched in terms that associated it with the newly emerging molecular biology). The reception of the model is a significant measure of the circumstances of the time; it was a tacit confirmation of Wolpert's attitude to induction. Even those who were critical of the PI model did not (as far as I am aware) comment on its relation to earlier theories and did not identify the specific problems arising. His impact owes something to the simple fact that he recalled what had (with the changes wrought on Spemann's reputation) increasingly been forgotten, namely the issues of pattern formation. It is an indication of the perceived "need" within developmental biology for some sort of general explanatory framework.

It is evident that a major constraint on the development of the subject was a factor external to it; the trend throughout biology towards reduction. Although I have concentrated on Spemann and Wolpert, they are in large measure symbolic of their times and situations. The course of events cannot in a simplistic way be laid at the door of specific individuals and their conscious decisions. Scientific developments were collective, diffusely influenced and only partly "deliberate". Many of the most important determining factors in explaining the historical sequence are likely to have been subliminal, both as regards the historical record visible to us now and also for participants themselves at the time. And yet, despite the undoubted "collective" aspect, any pattern of thinking (and especially a new one) can only really exist in the mind of the individual; therefore patterns of thought are ideally approached through a focus on individuals.

My main conclusion is that PI took over the position earlier occupied by the organizer, through a process that was largely a matter of re-occupying a theoretical and conceptual vacuum resulting from the marginalization of induction and the organizer. The general perception of the eclipse of induction had built up historically due to the accumulation of multiple apparent inadequacies. The core discoveries and facts remained, as we have seen, unchallenged and still valid - doubts concerned details -, but it was the general *perception* of inadequacy that mattered. As a succession of new techniques and priorities came and went the subject did not keep up methodologically, or "advance". In some, ill-defined, sense induction was seen as having failed - the approach had even been "wrong"; certainly Spemann's work came simply to seem "old-fashioned" and redundant. Hamburger sums up the general change of attitude that occurred by the 1960s as follows; "the dethronement of the organizer has been greeted with sardonic glee by some modern biologists who have tried to deprecate the significance of the organizer experiment and .... the chemical analysis of inductive agents" (Hamburger, 1988, p. 7).

2.3 Historical factors as determinants of conceptual change in science

The transition from organizer to positional information was not the result of systematic, logical argument and attention to the totality of the available evidence. This is clear from the fact that so little space was given to critically reviewing the concept of induction or to comparing and contrasting it with PI. The two concepts were apparently not even seen as comparable, but if they had both been presented together as new and on equal terms, it can hardly be doubted that the potential conflicts would have been spotted immediately. The detailed analysis in this paper has been presented with a specific aim, namely to show that in the active up-to-the-minute concerns of contemporary science - as can be well demonstrated within the present situation in developmental biology - some of the most basic issues are, in a sense, not matters of deliberate, "rational" consideration, but are better understood as the residual effects of largely forgotten historical backgrounds. In the previous section. I have described a number of "historical mechanisms" which bring about these historical effects.

In their training and objectives, scientists are not predisposed to thinking in terms of "historical" considerations, especially when it comes to the actual content of their current scientific interests, problems and conclusions. The activities of scientists are all directed towards sustained "progress"; in obvious contrast to the aims of historians, scientists are forward-looking and their targets are provable, new conclusions with potential practical application in the real world. Even where scientists and historians have overlapping objectives in the explanation and understanding of events, the ideal in science is for well-defined, simple and general explanations; historical explanations are each unique to the case and indefinitely complex. Scientists therefore naturally tend towards the narrowest window of concern with time past or with the earlier origins, as opposed to the present status, of the scientific issues. Yet the practice of science is unavoidably a historical process - a cumulative process through time - and subject to the effects of historical forces. Scientists may well be sceptical with regard to the less than ideal standards of "proof" that historians are condemned to live with in their explanations - the historian has to rely solely on the wealth of evidence, its coherence and plausibility. But in the experience of every individual scientist there is ample confirmation of the formative effects of "history"; i.e. in one's dependence, throughout one's career, on the formative experiences of one's early education, the chance effects of the contingencies of career path and so on. Every working scientist is, in this manner, intimately familiar with ways in which "history" can go to influence the direction and form of a scientist's work.

The scientific process is a historical one in the obvious sense that each new step is built up on the basis of knowledge and understanding already achieved. Much of this step-wise progression is logical and systematic - even mechanical and routine - and limited choices are involved. As part of the ongoing, forward-directedness of the process past data is, ideally, generalised and consolidated into laws, new concepts, general principles, applications, or rules of thumb, etc. In such a process, details of older data and historical origins are essentially edited out and ultimately forgotten. As we have seen above, there is a constant imperative to supercede, to modernize and to seek novelty. On the other hand concepts, theories or models - much more than detailed data - often retain their importance as explanatory building blocks over long periods (relatively invariant biological concepts like homology, adaptation, selection, gene, cell differentiation, species are examples). Embryology has, in the way described in this paper, been relatively unsuccessful in establishing a stable, generally agreed set of foundational explanatory concepts. (The few enduring generalisations such as "regulation" or "harmonious equipotential systems" are largely "descriptive" in kind, in the sense that they imply no specific explanations or mechanisms). And yet embryology is unusually dependent on its central concepts. It was the un-met need for an explanatory framework that made the introduction of PI possible. The organizer and PI concepts provided attempted encapsulations of the ways in which embryos were to be understood. Moreover they each determined the directions and priorities of research programmes. It is particularly at the level of concepts - precisely because, compared to raw data, they are complex and slow to evolve - that historical forces are most relevant. It is at these most basic levels of scientific thought and progression that the potentially distorting effects of history are likely to be most potent. So, I have focused specifically on ways in which historical considerations may have been real and significant contributors to the evolution of concepts in this subject.

One important side-effect of the onward, linear march of scientific advance is that, looking back, we find it difficult to recognise choices that existed along the way. There is the risk that we see science as following some intrinsically inevitable, even logic-driven trajectory; that it is a matter (allowing for a few diversions and hesitations) of uncovering truths in a sequence and pattern that is actually dictated by the structure of the reality of the external world it aims to understand. But realistically we must view past science in exactly the way that we regard present practice; choices have constantly to be made and small differences can occasionally have big effects later. Part of our problem stems from the fact that choices are difficult to detect in retrospect, simply because the alternative paths they might have led to are hypothetical. Even if the point is purely theoretical, it remains certain that developmental biology today would have been very different if different choices had been made during the history I have described.

In this paper my main focus has been concentrated on the single case history of conceptual change from the organizer to PI. In what ways can historical forces be said to have affected the actual form taken by Wolpert's model? A number of "assumptions" contributed to its delimitation; e.g. the perception of the "problem of development" in initially general and abstract terms (terms explicitly compared to Drieschian harmonious equipotential systems); reliance on the evidence from regeneration as a "model" for embryonic development; the unquestioned initial acceptance of Waddington's three categories (and the separating off of morphogenesis and other epigenetic intermediates which tended to go along with this); the framing of the model in the most reductionist terms possible. Wolpert's attitude to induction was largely an "assumption", in the sense that it did not seem to be an issue requiring explicit, rigourous scientific critique and rebuttal. As we have seen, each of these elements played a part in circumscribing the final model and each of them was effectively operating as an "assumption", that is they were brought to the initial situation as established facts or truths based on earlier history and therefore did not need justification; indeed they hardly needed stating and in some cases may only have been subconscious. PI was not arrived at in *direct* conscious opposition to induction, but indirectly the form taken by PI reflects the nature of the vacancy created by the historical failure of induction-based theory, and the need to be new and different. In this sense PI might be said to have acquired some of its distinctive features out of Spemann's legacy; the fact of its acceptance by the embryological community suggests a general perception that new "terms of reference" were necessary and realized in PI.

The effects of the way historical forces can dictate present-day science are perhaps shown most clearly in the way that the concepts of the organizer and induction evolved. In his time Spemann was a dominant scientific figure. His discoveries were regarded as outstanding achievements within the field of embryology. He was a pioneer and for this reason alone his perspective was the first defining statement of many of the issues to be pursued later; by 1924 Spemann had effectively set out all the relevant and important parameters for later exploration. But, as I have described, a variety of "choices" were available along the way; e.g. his emphasis on fields (at the expense of induction); his disregard of morphogenetic considerations (traceable back to his early concentration on "material" determination at the expense of "dynamic"). Somewhat harder to identify (but clearly voiced by Spemann) was his preference for a research strategy that emphasized whole embryo, "higher" level analysis (as opposed to the reductionist strategy, which he explicitly chooses to avoid, EDI, p. 2)[48]. We have seen how these particular lines of emphasis helped to determine the character of Spemann's theories. Given his dominant position, his ideas and his choices had direct effects on his successors; his concepts and perspectives set thinking throughout the period and well after his death. In the particular case of the role of cell movement, we have seen how Spemann's initial choice of emphasis (arising out of the alternatives presented in Vogt's work) had repercussions, not only on his own later work, but on Holtfreter and Waddington; and through Waddington on Wolpert. Irrespective of how considered and conscious these early influences were for Spemann himself, they had become deeply embedded later and eventually came to operate as unconscious layers of assumptions. A similar long-term chain of influence applies to the field concept, which we have traced back to ideas current around 1900 (e.g. privileged regions, assimilation). The evolution of the concept (and choices involved) took origin from inevitably "primitive" considerations, and even metaphorical ones. Here again we have a concept which has been immensely influential in the quite different contexts of later decades, but whose origins have long since been forgotten.

The main effect of historical forces for science - and the seat of the greatest potential distortions - is the progressive tendency for scientific concepts and conclusions to become detached from the arguments and detailed evidence on which their meaning and validity ultimately depend. To a large extent it is true that in science endpoint conclusions are what matters, quite independently from how they were arrived at. Once arrived at, concepts and theories are often cleaned up and re-expressed, especially through the simplifications and clarifications of textbook accounts. These therefore define the form in which the material is handed on down to succeeding generations of new scientists. Ultimately this process is liable to lead to a situation where the justifying layers of arguments and supporting data are entirely forgotten, justification is assumed and the surviving conclusions can no longer be subject to reasoned and critical assessment. Yet in *some* cases the justifications for conclusions may be entirely inadequate. The basis in early choices on which major trends of scientific thought and effort were founded may be entirely unjustified. In these ways then, scientific thought may be determined (and on occasion mislead) by considerations of which it may be entirely unaware. It is these sorts of considerations that must be invoked to account for the most extraordinary historical "choice" of all those I have touched on in this paper. I am referring to the replacement of organizer theory by PI. This transition illustrates just how an event, whose effects we still experience, can and must be understood as the end result of a vastly complex combination of long-term prior events.

Conclusions

How much, then, should historical considerations matter to scientists? There are many existing historical accounts of conflicts, delays and errors in the course of scientific advance - and even of occasional cases of temporary reversals of progress (e.g. the Lamarckian revival that briefly displaced Darwinism around 1900). Such accounts might well provide chastening lessons for scientists (Horder, 1998, Jardine, 2000). My analysis in this paper has sought specifically to examine - on the basis of one particular and, I believe, important case, examined in detail - some of the ways in which "history" impinges quite generally on everyday science in such a way that it can actually determine the content of scientific knowledge itself. The end result in terms of potential and unnecessary confusion is well illustrated, in the present instance, by the *simultaneous* appeal to both PI and induction that we now begin to find in some current textbooks and reviews. Without speculating on why or how the importance of induction and the organizer seem once again to have become acknowledged, I merely point out the depth of the confusion implied by the use together of what are essentially incompatible notions. This is a good demonstration of the potential effects of continuing failure to be aware of meanings and origins of concepts.

It is of course true that many aspects of science are little illuminated by history, especially day-to-day science. Much of scientific practice amounts to a mechanical working through of technique, and the vast bulk of scientific effort involves mere documentation and data accumulation. The historical processes and effects I have tried to identify impinge to the greatest degree at the most basic levels - at the level of concepts and especially the more "difficult" ones. Their effects are felt particularly at levels that most determine the direction and priorities of science. My embryological example may be an unusually complex case in many respects - the fickleness of the key concepts and the long time periods over which they evolve may well have something to do with the "complexity" and "difficulty of achieving integration" of theory and data that typifies biology - but there is no reason to think it is unique.

There are many reasons why historical factors tend to be invisible. This is not simply a matter of science being, in its aims, interests and practices, the opposite of "historical". Older texts are hard to "understand" and require special effort, especially to overcome what now appears as the "obscurity" of earlier, now unfamiliar forms of expression, which are easily misinterpreted. We tend, paradoxically, to be most blind to the largest scale and most basic assumptions within science, because they are complex but especially because they change slowly, to the point that the changes are imperceptible. The trend towards molecularization of embryology is a good example. It has taken on the characteristics of a unstoppable and self-fulfilling juggernaut, but it was built up only very gradually. It rarely seems to need any clearly expressed justification; it relies on a barely questioned reductionist assumption. Its side effects and limits are hardly mentioned, yet reduction cuts out higher levels of consideration; whole areas of biological evidence and study have been abandoned (Horder,1998). It is part of the tendency towards ever-greater specialization and narrowing in methods and horizons, which also seems to be characteristic of science. Where, one might ask, would one seek for mechanisms within science that provide correctives, discussion of alternatives or critiques to balance such trends? Holton (1986) notes another historical trend; how concern with "scientific method" has been gradually decreasing among scientists. Glass (1976) remarks on how, slowly, the "critical review article" has disappeared as a main device within science for achieving integration, for encouraging fresh ideas and for countering increasing specialization.

Being unattuned to the historical dimension, the procedures of science are poorly equipped to take historical issues into account and to make allowances as needed. Yet the sorts of errors and confusions which seem so obvious and unnecessary when we look back on earlier scientific episodes will eventually be equally evident and surprising to people looking back on today´s thinking. Inevitably distorting processes similar to those that I have described in this paper are still actively happening today. An awareness of the "historical dimension" is thus part of a fuller "self-awareness" by scientists regarding their procedures. Science involves the constant making of choices, some leading in worthwhile directions, others in what are ultimately regarded as "erroneous" ones. How are these judgements made and how can we optimize procedures in today´s science to avoid false trails? "Logic" is not enough; science is too complex, and there are no formal recipes for successful research "method". We have no other way of knowing which choice more closely approaches the "truth" than to await outcomes in the future. How else then can scientific method be judged other than on the basis of relating past practice to the outcomes in one´s present experience, that is by "learning from past history"? It is only as the result of an accurate and detailed understanding of historical cause and effect that one can acquire guiding principles (limited though they will always be) regarding the likelihood of achieving the intended outcomes through today´s scientific efforts. Thus an increased alertness to the historical dimension in science (and its effects and mechanisms) is part of increased awareness of the "methods" of science; this would entail an openness to exposing, questioning and correcting assumptions, an appreciation of the importance of judging new and older evidence on equal terms and a recognition of the importance of full examination and clarification of the meanings of key concepts.

I claimed at the start that this paper was as much a scientific contribution as a historical one. Hopefully it is now clear why I see history and science as inseparable. I have tried to demonstrate how a full clarification of concepts currently and freely used in today´s developmental biology entails a "critical reviewing" of the layers of data, arguments, assumptions, and older concepts that lie behind them and on which their meaning, validity and justification depend. Thus one is unavoidably engaged in a "historical" matter; "historical" procedures are involved if one is seriously concerned to examine and clarify one´s concepts. Realistically "science" must be acknowledged as being a historical edifice: it not only consists of the latest results, but, more accurately, it is composed of the sum total of a massive accumulation of earlier-acquired data, interpretation and assumptions.

Summary

This paper analyses the origins of the Spemann-Mangold organizer concept of 1924 in relation to his earlier background and concepts. It traces the consequences and fate of the organizer, and related concepts (embryonic induction, gradients, fields) through subsequent phases in the evolution of developmental biology up to the present, primarily from a UK perspective, but also in the USA. The origins of Wolpert´s concept of positional information of around 1970 are analysed; this markedly different model of embryogenesis effectively took the place of the organizer, following on from a generally assumed out-datedness of the corpus of Spemann´s data and concepts. Explanations in terms of historical forces are suggested; events are seen as a historical causal chain. A crucial factor appears to have been the long-term neglect of morphogenetic cell movement as an integral component of an adequate induction-based model. The paper discusses the general inter-relation of history and science, and particularly the implications for current scientific practice, including the potential for conceptual distortions due to historical factors. It is argued that historical considerations need to be included as part of the use and critical assessment of basic concepts in science.

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Notes

1. In embryology the exact definition of terms is often difficult; key terms frequently have abstract meanings with important but unstated associations which may be different for different authors. As Oppenheimer points out (1967; p. 182) words have often been imported from other scientific disciplines (e.g. engineering, physics, and psychology). A few older texts include glossaries; Needham, 1942; Lehmann, 1945. Valuable commentaries on the origins and definitions of selected key terms can be found in; Woodger, 1929; Needham, 1929, 1931, 1942; Oppenheimer, 1967; Churchill, 1969. Difficulties in understanding Spemann are compounded by the additional problems arising from translation from the German. I have confined myself in this paper to quotations from standard translations (i.e. Spemann, 1938 and Spemann and Mangold (1924, in Willier and Oppenheimer, 1964), including Hamburger's, 1988, re-translations); in each case page references refer to the translations, not the original German papers. Horder and Weindling (1986) list some of Spemann's German terminology, as do Hamburger, 1988 and Fässler,1997.

2. COMPETENCE. The particular (sometimes restricted) state of reactivity or "potency" of cells prior to undergoing induction. Coined by Waddington in 1932. Partially overlaps concepts of "*Bahnung*" (facilitation; Vogt 1927-8), "pre-determination", "labile" or "reversible determination", all of which imply that reacting tissue is already disposed towards a certain pattern of differentiation. Spemann talks of the reacting system as being "charged " for a specific response (EDI, p. 370). Entirely uncommitted tissue is termed "indifferent", multipotent, equipotential. On difficulties in the concept of potency see EDI, p. 190-198, 199-212, 341, 345. See further; H, p. 78; HW, Notes 53,55.

3. DETERMINATION. The fixation of the fate of a cell. Since determination involves a loss of "potency"; the two concepts are inextricably linked. A particular difficulty with the concept has been that defining the state of determination is dependent on the assays used (see Harrison, 1933; EDI, p. 110-118, 190-198, 204-212). The older term "segregation" (later promoted by Lillie, 1929) corresponds. Cf. Weismann's "determinants", Spemann's "determination stream"; "determination field". The state of "being determined" overlaps the concepts of "self-differentiation" or "mosaic development" or "mosaic stage of development". To be contrasted with "differentiation", the later visible histological outcome of determination; Spemann often used "differentiation" and "determination" interchangeably (Fässler, 1997, p. 237).

4. DOUBLE ASSURANCE. The collaboration of multiple causal factors in reaching determination. Term taken from engineering by Rhumbler and Braus (1906). Noted by Spemann in 1907 but first used by him to explain the species variations and multiple factors in lens induction in 1927. From 1933 he preferred the term "synergistic inductor systems". Reviewed by Lehmann in 1928 (EDI, p. 92-7, 189,197) and 1933 (see H, p. 67-74)

5. EPIGENESIS. The gradual emergence of pattern as a direct result of the processes of development from a starting point relatively lacking patterning. To be contrasted with the concept of "preformation". Waddington re-introduced the word to emphasise the link with, but distinction from, genetic factors and to highlight the operation of factors due to interactions within the developing embryo above the preformed gene level.

6. EVOCATION. "induction-as-such" (Waddington, 1956, p. 188). As distinct from "individuation", "the formation of an organised structural entity" (Waddington, 1956, p. 188). Both terms coined by Waddington (1933-4) to distinguish distinct aspects of induction; evocation is the result of heterogeneous chemical stimuli and triggers cell differentiation in absence of tissue form or organization. Individuation is a field phenomenon (involving surrounding or host tissue) which establishes regionalisation and spatial patterning of tissue. "Individuation" is a psychological term (Waddington, 1966, p. 106). Parallel distinctions were made by Lehmann, (1933), Dalcq, Nieuwkoop ("activating" and "transforming" principles).

7. FATE MAP. The normal prospective developmental outcome of different cells as mapped in early (pre-differentiation) developmental stages, e.g. by vital dyes. Cf. "germinal localization" and Driesch's "prospective determination", "presumptive value". Americans prefer "prospective", British "presumptive" (Waddington, 1956, p. 158). Closely related to concepts of promorphology and lineage tracing[34].

8. FIELD. "transient embryonic units that are self-differentiating as a whole but regulative within their boundary. ....Any part can substitute for other parts and ...a fragment of adequate size can reconstitute the whole" (H, p. 134). Sometimes "all that is meant is a reference to the geographical location in which something is happening" (Waddington, 1956, p. 23); "the term "field" is used to emphasize the coordinated and integrated character of the whole complex of processes" (Waddington, 1956, p. 416); "pattern formation and morphogenesis are typical examples of field phenomena, since they involve processes which are both extended throughout a region of space and which also have a certain unity" (Waddington, 1956, p. 25). "the term that replaced Driesch's harmonious-equipotential system" (H, p. 129). The term, taken from physics, was first used in this biological sense by Spemann (1921; p. 568 as "field of organization") and Gurwitsch (1921) (Bertalanffy, 1933; Weiss, 1935, p. 654). Spemann had used the term "*Feld*" even earlier (e.g. in his 1918 paper) in connection with the grey crescent and in 1903 (p. 503). Classic examples; limb (development and regeneration), eye (lens regeneration). The term "system" corresponds. Cf. "determination field" "morphogenetic field", "positional field", "gradient-field", "individuation field". See further; Huxley and DeBeer, 1934; Weiss 1939; Needham, 1942, p. 127-30; Waddington 1956, p. 23-8; Oppenheimer, 1967, p. 15-6; Herrmann, 1964; Haraway, 1976, pp. 54-62, 177-9; Opitz, Reynolds and Spano, 1986, HW Note 55.

9. GRADIENT. A quantitatively varying parameter extended across an embryo, as a possible determinant of later spatially organized differentiation. "a system of order involving progressively increasing or decreasing entities or intensities from one pole or point of a morphogenetic field to another" (Needham, 1942, p. 684). Word first used in context of regeneration by Morgan (1904, 1905), in context of embryonic development by Boveri (1910); reviewed by Child in 1906 and taken up by him in Child (1911). For history see Oppenheimer, 1967, p. 11-15; Haraway, 1976; Wolpert, 1986, 1991.

10. INDIVIDUATION, see EVOCATION .

11. INDUCTION. "one tissue calls forth specific formations in an adjoining tissue" (Weiss, 1939, p. 273). The word was not commonly used until the 1930s. For many early workers synonymous with the action of an organizer (and may include both evocation and individuation). In the narrower, more recent, sense it refers to the specific cell to cell interaction which initiates and locates the train of events that result in final differentiation of responding cells. "the commitment of an embryonic tissue or structure to a particular developmental fate as a consequence of influences from its environment, usually understood as emanating from another closely associated tissue or organ" (Saunders, 1970, p. 253}. For Spemann synonymous with "organizer". Classic examples; lens, neural plate. For early history see; EDI, p. 222-4; Needham, 1942, p. 103-11; Oppenheimer, 1991.

12. MORPHOGENESIS. The word "morphogenesis" has been used in so many different and loose senses (Waddington 1970, p. 193-96) that it is best avoided. It has been used as a synonym for "pattern formation" (as in "morphogenetic field", i.e. describing the entire developmental process) or to describe one specific aspect (as distinct from differentiation and individuation or pattern formation), e.g. "the moulding of a mass of tissue .....the forming of a mass of cells into a new shape" (Waddington, 1956, p. 12). However, the phrase "morphogenetic cell movements" captures the notion that cell movements (including migrations, foldings, aggregations and the effects of mitosis or cell death) are essential

components in the epigenetic chain of events and intimately connected with ultimate morphology.

13. MOSAIC DEVELOPMENT. Component parts of the embryo are already fixed in their fates from an earlier or initial developmental stage; when isolated those parts differentiate according to their prospective fates. Closely related to "preformation". To be contrasted with regulative development.

14. ORGANIZER. "A living part of an embryo which exerts a morphogenetic stimulus upon another part or parts, bringing about their determination and the following histological and morphological differentiation. The organiser which acts first in development is known as the primary or first-grade organiser" (Needham, 1942, p. 686). First coined by Spemann (1921) to refer to the action of the dorsal lip of blastopore, which remains the classic example. For some time used synonymously with "induction" (hence "organizer of the lens", etc). "Organizer centre" refers to the normal area in the embryo containing tissue having such actions. Terminologically overlaps "field", or "self-organization" (H, p. 134-6)[37].

15. PATTERN FORMATION. The organized developmental laying out of differentiated cells in space. Term used by Waddington (e.g. 1956) to describe aspects of individuation other than those involving morphogenesis.

16. POLARITY. A directionality inherent equally in all parts of a developing or regenerating tissue, such that each part can differentiate with one end distinguished from the other. A difficult term, based on the magnet analogy, closely related to those of "gradient", "dominance", "privileged region" or "preference region" and most common in the regeneration literature. Cf. "axiation" (Huxley and DeBeer, 1934, p. 82) See further; Oppenheimer, 1967, p. 11-2; Harrison, 1969, p. 197; Wolpert, 1986, 1991.

17. POSITIONAL INFORMATION. "A coordinate system with respect to which the cells have their position specified. The cells then interpret their positional value by differentiating in a particular way" (Wolpert, 1989, p. 3). The term was introduced by Wolpert in 1968.

18. REGULATION. The power of continuing normal development despite earlier removal or displacement of embryonic parts. Driesch introduced the word in an embryological context from physiology (l891). Driesch's "harmonious equipotential systems" are characterised by ability to regulate. To be contrasted with mosaic development.

19. The sources and literature references listed in this paper are very selective. Details are given for British embryologists, but few for American and German or for the earlier history. For more specific sources on the literature, see Horder, Witkowski and Wylie, 1986; for general background on the 19C background, Russell, 1916; Nordenskiöld, 1928; Coleman, 1971; on the British embryological tradition, Ridley, 1986; *Int. J. Dev. Biol.* (2000) Vol. 44, No.1 "The Spemann-Mangold Organizer" Special Issue; on the divergence of genetics and embryology, Wilson (1925) and earlier editions), Thomson, 1912; Allen, 1986; for detailed, historically informed accounts of the scientific issues; Dalcq 1935, 1938; Huxley and De Beer, 1934; Needham, 1942; for pre-war personal reminiscences, Goldschmidt, 1956, 1960; Twitty, 1956; Holorenshaw, 1973; Seidel, 1981; Holtfreter, 1991; Hamburger, 1988, 1996; Waelsch, 1992; see also obituaries; Spemann, 1941; Hyman, 1957; Baker, 1976; Newth, 1982; Bagnara, 1993. For sources of detailed information on Spemann, see Horder and Weindling, 1986. O. Mangold's standard accounts on Spemann have recently been significantly supplemented by Hamburger, 1988 and Fässler,1997, who lists most of Spemann´s papers.

20. Julian Huxley (1887-1975) was a student of Jenkinson and Geoffrey Smith at Oxford; worked with Warburg and R. Hertwig (1912); Lecturer in Zoology, Oxford (1911-2; 1919-1925), Professor of Zoology, Rice University, Houston, Texas (1913-1916), Professor of Zoology, Kings College, London (1925-7). Like Child, Huxley was also much involved in studying animal behaviour. Introduced concepts of "growth-gradients", "rate genes" and allometry. Thereafter left academic and research life; increasingly occupied with popularising science and public life. First Director of UNESCO, etc. G.R. De Beer (1899-1972) was Huxley's student; Demonstrator in Zoology, Oxford; later Director, British Museum (Natural History). See Baker, 1976; Churchill, 1992; Morrell, 1997. Both Huxley and De Beer turning from embryology to evolutionary issues after 1934.

21. Joseph Needham (1900-1995) spent almost all his student and working life in Cambridge; from 1920-1942 based in the Dept of Biochemistry under Hopkins; best known for a wide range of biochemical approaches to embryology; the encyclopaedic "Chemical Embryology" (1931) was followed by "Biochemistry and Morphogenesis" in 1942; thereafter left scientific research for work on history of science in China. See Holorenshaw, 1973.

22. Conrad Hal Waddington (1905-1977), having studied geology/palaeontology and considered genetics, began research on the avian (and later mammalian) organizer in about 1929 at the Strangeways Laboratory, Cambridge (which provided expertise on the avian embryo and tissue culture, De Beer had exploited this earlier, and Huxley (with Murray) also studied embryo grafts of avian tissue in the late1920s); by 1933 he was collaborating with Needham on the chemistry of the amphibian organizer; a switch towards *Drosophila* genetics is evident in "An Introduction to Modern Genetics" (1939) and "Organizers and Genes" (1940); from 1945 - 1970 he was head of the largest UK genetics department, in Edinburgh; his work on "genetic assimilation", alongside his favourite genetics-embryology-evolution hybrid concept of "canalisation" can be seen as part of the "modern evolutionary synthesis". Disregarding Waddington's own "Epigenetics of Birds" (1952) (a specialist treatment of mainly pre-war avian embryology) his "Principles of Embryology" (1956) was the first post-war, general embryology textbook in the UK. See Waddington, 1975; Robertson, 1977; Yoxen, 1986; Stern, 2000.

23. Lewis Wolpert (1929-); doctoral student, Kings College, London, 1956-60; Assistant lecturer, lecturer, reader, Dept of Zoology, Kings College, London, 1958-66; thereafter Professor, Dept of Biology as Applied to Medicine, Middlesex Hospital Medical School, London.

24. Wilson maintained interests in both development and genetics, as shown in his classic volume "The Cell in Development and Heredity" (first edition 1896, last 1925). He favoured a promorphological approach. Until 1910 Morgan worked on embryology, regeneration and evolution (with approaches closely comparable to those of Child or Loeb). After 1928 he returned from *Drosophila* genetics to experiments in embryology; his position is summed up in two large review volumes (1927, 1934). Russell (1930) well illustrates the continued dilemmas confronting both genetics and promorphology within embryology.

25. Spemann has sometimes been accused of lacking an interest in genetics. This is not strictly accurate, especially given the distinctively "holistic" and "physiological" approach to genetics in Germany (Harwood, 1993). He wrote a paper on general genetic problems (1924); he experimented on the equivalence of daughter nuclei during cleavage; he was much concerned with the implications of cross-species tissue interactions; in EDI there are innumerable references to Weismann, idioplasm and the "hereditary factor". See H, p. 43-4; Fässler, 1997, p. 310-314.

26. On different national research traditions in embryology, see Oppenheimer, 1955, 1966; Churchill, 1981; Horder *et al*., 1986 (introductions to chapters); Maienschein, 1986; Benson,1988; Keller, 1995. On the history of the sea-urchin as a research object, see Horstadius, 1975;. Ernst,1997.

27. Sympathetic and detailed treatments of Driesch's incisive and much respected scientific contribution are given in Jenkinson, 1909; Needham, 1942. Driesch invoked the idea of polarity (and magnets) to explain how future patterning could be latent in harmonious equipotential systems; he appears to have avoided the gradient approach. For Driesch's final vitalistic position; Driesch, 1929.

28. Postgeneration is a regenerative mechanism proposed as an explanation for cases of embryonic regulation; after removal of parts of it, the remaining embryo behaves as a mosaic (as described by Roux), but secondarily regenerates the missing parts (yielding a complete embryo as described by Driesch) (EDI, p. 142-3, 347). The argument that regeneration disproves Weismann's "germinal selection" theory was countered by the concept of "reserve idioplasm". Roux drew another widely accepted distinction (which had Lamarckian undertones) between early "pre-functional" stages of development, and later "functional" stages - when adult-type physiological forces and external stimuli directly accounted for morphology (as in the shaping of bones or blood vessels).

29. Charles Manning Child (1869-1954) graduated from Wesleyian University in zoology; Ph.D. at Leipzig (under Wundt and Leuckart); Dept of Zoology, University of Chicago, 1895-1937, where he was eventually head. See, Hyman, 1957; Twitty,1966; Haraway, 1967, p. 53-5; Oppenheimer, 1967, p. 10-17; Kingsland, 1991; Mitman and Fausto-Sterling, 1992. For his final views on the organizer, see Child, 1946.

30. Huxley began a correspondence with Spemann from late 1923 or early 1924 (Churchill, 1992; Fässler, 1997). De Beer visited Freiburg in 1926 (Haraway, 1976). Waddington visited Freiburg in the late 1920s (Fässler, 1997). According to Haraway (Haraway, 1976, p. 116) in 1931/2 Spemann discouraged a collaboration with Waddington, who then went to Mangold and Holtfreter in Berlin (Robertson, 1977; Yoxon, 1986); he collaborated in a paper with Spemann's colleague, the Russian G. Schmidt. Needham visited in 1933. A number of American embryologists also visited and worked with Spemann or Mangold, including Detwiler, E.G. Hall (in 1928), Kitchin, Copenhaver, Adelmann (late 1920s), Twitty (Berlin, 1931-2) and Eakin (Freiburg in 1935/6 when he helped in the translation of Spemann's book (Eakin, 1975). Harrison and Spemann met many times; Harrison visited Freiburg in 1928 (Fässler, 1997).

31. I will discuss the 1924 paper as though Spemann was the sole author on the assumption that it reflects mainly his thinking.

32. To the extent that Spemann regarded the two mechanisms as complementary and subject to a single initial organizer mechanism, no hard and fast distinction was called for.

33. First mooted in 1903 (see EDI, p. 159) and reiterated in Spemann's 1918 paper. In this paper (pp. 531-33), he is already clearly aware of the two possible mechanisms. In the 1924 paper Spemann identified the first mechanism directly with the process of gastrulation itself (visible morphological events, particularly the formation of the blastopore, were of interest at the time; they would soon extend into Vogt's studies of "dynamic determination")[46]. (The second (and later continuing) mechanism he linked to "assimilation"[36] and the ability of the embryo to complete itself through regulation and/or postgeneration. Spemann used the regulative behaviour of the blastopore as a key example of assimilation).

    Regarding the exact origins of concepts and timing of events (summarized earlier in tabular form), and the possible causes of delays, information is limited. There was often a gap of several years between an experiment and publication; this makes it difficult to know how much earlier than the publication dates Spemann's new concepts might have emerged. (Typically Spemann published a review lecture before the definitive paper, Fässler, 1997, p. 236). Spemann's work was hampered in the period 1919-24 because of his move from Berlin to Freiburg (H, p. 46) and illness (H, p. 23). His first use of the heteroplastic technique is uncertain (HW, Note 35). The technique was technically demanding and successes relatively few; the 1921 paper mentions only 8 specimens, none of which happened (perhaps by chance) to come from near the blastopore (unlike specimens in the previous homeoplastic series). The Petersen letter has been lost and its date (in response to a paper in 1918; probably in late 1918 and no later than March 1919) has to be inferred (Fässler, 1997, p. 246). It is not clear what Petersen said (see Spemann's 1921 paper, p. 550; H, p. 46; EDI, p. 143; Fässler, 1997, p. 246, for evidence on its contents). Spemann's inauguration lecture (1919) probably took the letter into account; it distinguishes clearly between the two routes for the effects of the "differentiation center" in causing neural plate formation (see H, p. 31 for quotation). It remains unclear why, after receiving the letter, he waited for two operating seasons before asking Hilde Mangold (neé Proescholdt) to perform the final experiment, and a further 2 years before submitting the 1924 paper; a certain lack of urgency is suggested, or a reluctance to deflect from his earlier systematic experimental objectives.

34. The history of fate mapping (a term that only became current in the 1940s) can arguably be traced back to His' theoretical concept of "organ-forming areas". See, Jenkinson, 1909; Morgan, 1927, p. 227-32, 1934; Vogt, 1929; Spemann, 1941; Oppenheimer, 1955, p. 32, 1967, p. 27-8, 1970; Maienschein, 1986. Lineage tracing achieves the same result but is only readily applicable in small, transparent and rapidly developing embryo types. Vogt published his first amphibian maps in 1923, with the full account following in 1929, using vital dye methods (which had been available since around 1910). Prior to this, direct evidence was limited and conflicting (see Sander, 1991). Spemann makes it clear, in his 1918 and 1924 papers, that he is aware of the potential of his grafting methods to be used to construct a fate map. He eventually corrected his earlier misunderstandings about the neural plate fate map, but without comment (EDI p. 163).

35. Why did Spemann fail earlier to make the deductions pinpointed eventually by the Petersen letter in 1918/9? Before this time all the relevant concepts were available to him. He had already referred to neural induction by mesendoderm (1903) and to formation of mesendoderm through the invagination of gastrulation (1918; quoted, H, p. 33; 1921, quoted, H, p. 46-7; H, p. 55). In 1901 (H, p. 14), he had envisaged a "dorsal agent" ("*Differenzierungssubstanz*") being transfered from one region (dorsal) to another (ventral) to allow determination and differentiation. Spemann started his early work from a position assuming that control of pattern was already established in the egg stage; however his work progressively uncovered how determination actually occurred much later within the ectoderm and probably within mesoderm (although less so in endoderm). In all his earlier graft transplantation experiments his aim was to use the criterion of self-differentiation in order to map out spatio-temporal patterns of determination; even in 1924 he was still uncertain whether neural plate differentiated in antero-posterior or postero-anterior sequence (SM, p. 176). He therefore had no reason to look for, or to be interested in, interactions by the graft with neighbouring host tissue. In the case of homeoplastic grafts (where he obtained an organizer effect in 1916) the method would not have allowed him to detect such interactions; moreover the three secondary embryos obtained were small and unimpressive (e.g. Figure 77 in EDI). Given his unconcern with fate maps, he had no reason to question the assumption that the secondary neural plate was graft-derived; besides, he had doubts as to whether the grafted blastopore developed normally once transplanted to a foreign location (a concern that proved correct; later he discusses how the graft itself regulates, SM, p. 174, 179; HH, p. 179-180)) Prior to the letter he would have seen the blastopore primarily as a convenient and essential marker of position on the surface of the embryo; he had no reason to think of it in terms of its "function", i.e. in gastrulation.

36. The close correspondence between the field concept and the earlier one of assimilation is best recognised in the similarity of the way the supposed mechanisms are described; Spemann's phraseology in the 1924 paper describing fields matches remarkably what he had already said about assimilation. The general notion of assimilation can be traced back to Roux in 1888 (EDI, p. 143). Spemann invoked a similar (and "cherished" (H, p. 33), see also Fässler, 1997, p. 238-47) principle in about 1898 in the context of ear development and postgeneration (EDI, p. 142-3), terming it "growth by addition" (*Andifferenzierung*) (1903) (H, p. 30) - "growth" here covers differentiation - to refer to situations where differentiation spreads across, and gradually incorporates, pre-existing arrays of uncommitted embryonic cells (in contrast to situations where new cells are added among or near already differentiated cells ("expansive growth")). He invoked the same idea (now termed "appositional growth") in explaining the influence of the "differentiation center" as it extends over the embryo (1918) and in explaining the perfect structural integration of host and graft tissues in the organizer effect. He later applied the term "assimilative induction" to the concept (EDI, p. 163-6, 198, H, p. 54; HW Note 55). The concept is probably subsumed within the still later but similar notion of "complementary induction" (EDI, p. 279-83). Spemann seems to have been particularly impressed by the assimilation occurring within mesodermal (alongside neural) structures (EDI, p. 163). A number of Spemann's terms and analogies throw light on how he envisaged assimilation[45].

37. Spemann first introduced the phrase, the "problem of organization" in 1901, and used the word "unorganized" in 1900 (Fässler, 1977, p. 175). For early uses of the word and concept of "organization", see Child, 1911; Woodger,1928, p. 257, 288-317; Harrison, 1937, p. 2; Fässler, 1997, p. 248-9. Morgan (1904, p. 747) referred to "organization power". The word "organizer" seems not to have been used after 1921 until it appeared in the title of Spemann's 1924 paper; in 1924 Vogt refers to the phenomenon but does not use the word. Spemann (1924; EDI, p. 156, 162, 224) insists on an important distinction between "organizer" and "organization centre". The latter term had emerged in 1919 as a replacement for "differentiation centre"; it refers to a *location* of a region in the embryo. [In the 1924 paper, p. 182-3, he still uses the phrase *"preferential (e.g. privileged) region"*]. By contrast the "organizer" is the actual mediator of progressive patterning across the whole embryo. In the 1924 paper (p. 182) the centre is seen as containing *multiple* organizers; this probably reflects Spemann's notion of an internal "structure" within the organizer[42], which provides it with the means to control all aspects of embryo pattern; orientation, size, laterality, etc.

38. On the history of theoretical biology see, Driesch, 1929; Bertalanffy, 1933; Needham, 1936; Haraway, 1976; Werskey, 1978: Abir-Am, 1991; Alt *et al.,* 1996; Hopwood, 1997.

39. On the timing of the writing of the book and its coverage of the literature, see HW, p. 195-6.

    In general terms the book follows the chronological sequence of Spemann's scientific career, but for ease of comprehension some material (e.g. the later lens data (Chap. 4), and the presentation of fate maps in Chap.1) is included out of historical sequence. This also applies to Chap. 5, which is presented before the account of the organizer discovery, presumably because it deals with "early" gastrula stages prior to the time the organizer acts. Though complex (and made even more difficult through lacking an index), the book stands as the most definitive and thorough presentation available on vertebrate experimental embryology in the pre-war period, notable for the wealth of experimental data it makes available.

40. For a listing of Spemann's references to neural induction by mesendoderm see HW, Note 55.

41. In 1926 Huxley undertook an experiment which related directly to Spemann's work. He subjected an amphibian embryo to a temperature gradient, expecting that this would differentially affect metabolism and thereby disturb development as predicted by Child. Gilchrist and Vogt (for different reasons) did the same experiment around the same time (EDI, p. 333-44)

42. "At the beginning of gastrulation, the individuality of the embryo is represented, so-to-speak, by the cells of the upper blastoporal lip which represents the organization center; starting from it, the most important other parts of the body are formed" (Spemann, 1919, see H, p. 12)

43. Already in Spemann's 1921 paper (see EDI, p. 259), and indeed earlier, induction was considered as a release of potentialities (rather than as an instruction) on the

grounds that the responding tissue showed species specific features that could not have been due to the inductor itself, which was derived from a second species (H, p. 41). These issues were later followed up in EDI, Chap.17.

44. That Spemann saw fields as equivalent to organizers is suggested by his uses of the phrases "organizer field" and "field of organization" (Spemann, 1927, p. 180; EDI, p. 297).

45. On Spemann's views on the chemical approach to induction, see H, p. 92, 140-143. Spemann often seems to compare and contrast chemical with physical factors and to favour the latter as possible bases for organizer action and fields (HW, Note 55). He associated organizer action with energy "flow" (EDI, p. 331-2), "an organizing force" (p. 147), "resonance" (p. 321), or "the transfer of a physical condition" (p. 158); "there is included ..... those physical factors such as tension, electrical states, and rays" (p. 303); "an "organizing current" issuing from the blastopore lip. .....it might.... act ..... merely by spreading in the surface" (p. 187-8). For other contemporary views on the physico-chemical basis of development, see Needham, 1936; Harrison, 1969; Haraway, 1976.

46. The relationship between Spemann and Walther Vogt is particularly interesting and important (see Spemann, 1941; H, p. 60-1, 71-2, 75-81, 107-8). Their work intersected in many respects. Vogt (1923) uses phrases (EDI, p. 125-32) close to Spemann's; e.g. "field of force", "current of determination". Although Spemann evidently shared Vogt's views up to a point (best shown in EDI, Chap. 5), they differed on several fronts. Vogt's essentially preformationist position, originally based on his evidence concerning "dynamic determination", was later expressed through the concept of *Bahnung* which invokes a time-linked facilitation of a developing cell's progression towards a state of determination. Spemann favoured the concept of "labile determination". Vogt was sceptical of aspects of Spemann's results because he believed that experimental interventions created artefacts. To circumvent these, he ingeniously attempted to replicate Roux's mosaic findings without surgical intervention, using temperature gradients to produce an "age chimaera". His vital dye method of fate mapping successfully avoided the artefacts involved in earlier more interventionist methods. Vogt's early distinction between "dynamic" (i.e. morphogenetic movements) and "material" (i.e. cell differentiation) determination may have been important, at a crucial time, in allowing Spemann to disregard morphogenetic considerations. While himself focusing on the "material" aspects of determination, Spemann may, effectively, have left dynamic aspects to Vogt, together with fate maps, the prime evidence for cell movements. Hamburger interestingly hints that Spemann may have chosen to underplay his doubts about Vogt's position (H, p. 78-9).

47. Kurt Goerttler, Vogt's student (working after 1926 with Mangold), attempted experiments (1927-1931) designed to show that "dynamic determination" was in itself the cause of later "material determination", in other words than prior morphological properties of embryo tissue controlled differentiation. His results were disconfirmed by Geinitz (H, p. 71) and Holtfreter. Spemann addressed these claims at a number of points throughout his book (EDI, p. 118-23, 158-9, 205-7, 224-5, 344; Chapter 8, part 3) but usually only to rebut them; he was sceptical and critical (H, p. 71)

48. Spemann invariably presents his material in a scrupulously logical manner; he habitually juxtaposes alternatives and often insists that the data do not yet strictly allow final decisions regarding several possibilities. His hypotheses are constantly defined in terms of the experimental tests that would be necessary to prove them; this explains how he often suggested the crucial experiments well before they were attempted. It is "self-evident....(that problems).... must be treated from the standpoint of strict causation" (EDI, p. 1). He denied being a theorist (EDI, p. 367-8; H, p. 95; 131-2; Fässler, p. 115-42). He insisted that the organizer concept was only "preliminary" (EDI, p. 368) and by 1938 considered that his original concept had become "problematical" (p. 369) and required "certain restrictions" (p 368). Spemann's comment (p. 369), "A *dead organizer* is a contradiction in itself", when interpreted in context, can be seen as a statement of his belief that organizer and field phenomena are properties only demonstrable in the living state, in marked contrast to the limited effects that can be attributed to devitalised tissue or chemical factors. The final paragraph in his book is in part a commentary on the inadequacy of the chemical approach ("a common chemical reaction"). On the psychic analogy, see HW, p. 217-9; H, p. 11. Its importance to Spemann is suggested by the close way he links it to fields; when formulating the field concept he was "remindful of psychical facts" (EDI, p. 303). On vitalism, organicism and related concepts, see Neal, 1916; Driesch, 1929; Needham,1929; Woodger, 1929; Bertalanffy, 1933; Bautzmann, 1950; Hein 1972; Haraway, 1976; Roll-Hanson, 1984. Spemann was well aware of "vitalism" and Driescb's association with it (EDI, p. 37). In the USA Lillie promoted a strongly organicist position (Lillie, 1938).

49. Waddington consistently divides embryology into the three categories; differentiation, pattern formation and morphogenesis (e.g. Waddington, 1956, p. 11). The latter two he lumps together as "individuation". His evocation/ individuation distinction[6] goes back to Waddington's earliest embryological work; it came at the height of the first discoveries on the chemistry of induction. One can speculate about ways in which there might have been linkages between Waddington's distinction and Spemann's duality of organizer mechanisms; certainly individuation is close to the field concept. Indeed Waddington often uses the phrase "individuation field". The evocation/ individuation distinction (criticized by Holtfreter, 1951; HH, p. 259-63; H, p. 146, 169-70) may have associations with Strangeways (Needham, 1942, p. 514) and Needham's concept of "dissociation" (Needham, 1942, p. 505-531; Weiss,1935, p. 643-4; "this is the only stand one can safely take", Weiss, 1935, p. 667). Such distinctions "led to a dead-end road" (H, p. 146).

50. HH, p. 279. See also, Huxley and De Beer, 1934, p. 134-140; but see Needham, 1942, p.162.

51. In the post-war period, studies of neural induction effectively took the place of work on the organizer as such. There was a general tendency to concentrate on specific organs (at the expense of the whole embryo), a trend that was reflected in the layout of textbooks; see Willier *et al.*, 1955; De Haan and Ursprung, 1965. There was increasing evidence for the complexities of the causal interactions that occur *within* organs; Coulombre (1965) is a notable example showing how it is possible to unravel developmental causal factors in a particularly complex organ, the eye. In Willier *et al.* (1955) (p. 252-3, 370-380) the development of the morphology of the neural tube is treated in a comparable way; its final differentiation is shown to be dependent on multiple secondary epigenetic interactions (earlier descriptions of Lehmann's work were given by Spemann, EDI, p. 176-181). Similarly Hinchliffe and Horder (1993) presented limb developmental as an epigenetic cascade. They pointed out how, in many respects, the limb bud is a potentially unrepresentative and misleading model for development generally, because its characteristics are dominated by the group behaviour of mesodermal cell masses; inductions are hard to investigate in this situation and few typical inductions have been demonstrated in the limb.

52. On views on embryonic cell movement in this period, see Oppenheimer, 1967, p. 27-9, p. 31-3, 1970; Abercrombie, 1977; Newth, 1982.. For earlier views see Jenkinson, 1909; Morgan 1927, 1934. Wilhelm His' early emphasis on mechanical forces in the embryo may, due to the almost caricaturing effect of his modelling approach, actually have inhibited later serious interest. Abercrombie (1977) discusses a long-standing "resistence" of embryologists to notions of morphogenetic cell movement, which he attributes to an earlier over-emphasis on mitotic tissue growth.

53. The organizer region may owe its special properties to the fact that it is the first step in the epigenetic cascade; for this reason alone it has, uniquely, influences on all aspects of later development throughout the embryo, but in other respects it is no different from other centres of morphogenetic movement leading to cascades of inductions. However, the current molecular biological focus on the organizer seems to imply an expectation of unique molecular features to the region. It has yet to be demonstrated that the molecular approach can "solve" either this question or definitively characterize any induction. Molecular definitions are singularly inappropriate for studying phenomena depending on coordinated movements in groups of cells. If the organizer or any inductive interaction are viewed as *processes* (a sequential complex of events and causes), then molecular approaches can be seen as offering only a selective and probably restricted view in what they can reveal.

54. On reductionism, see Horder, 1993. With the reductionist programme it is hard to avoid the implication of single-factor causality and the assumption that the identification of a specific chemical or physical entity is the only legitimate basis for definitive explanations in biology. "There was a marked tendency to single out one individual factor as responsible for determination" (Weiss, 1935, p. 643).

55. This paper has primarily focused on the UK, but I have alluded to many correspondences and comparisons regarding the USA. It would be hazardous to generalise about overall differences; embryology in the USA was divided into a number of quite distinctive schools, dependent particularly on the species studied (e.g. Harrison favoured amphibia, the cell lineage school and Child favoured invertebrates, and a strong focus on chick embryology originated under Lillie and Willier). The nearest equivalents to the European "experimental embryologists" were Harrison and Child. Despite the large number of contacts and exchanges between the USA and Germany[30] - and the evident admiration for Spemann´s work - it is notable that almost no work was undertaken in the USA on the organizer prior to the 1960´s or on induction and the chemistry of induction. (The only sustained interest pre-war in the early amphibian embryo came from Barth and Boell, whose emphasis was on metabolism; Harrison rarely uses the induction concept and only once addressed induction experimentally (HW, Note 101)).

Possible reasons include the following; despite its differences Child´s work seemed already to address the broad general classical issues covered by Spemann; Harrison and his school concentrated on later developmental stages (and on specific organs); in contrast to Spemann´s emphasis on the whole embryo and germ layers, American embryologists were characteristically cell-centered (this feature started with the cell lineage tradition and is well seen in Wilson and in Harrison; through the 1930s there was a remarkable consensus of approach showing clear anticipations of post-war cell and molecular biology; see especially, Needham (1936) and Harrison (1969, Chapter 1) and general survey by Haraway, 1976); a final factor was the effect of the influx of European immigrants (Paul Weiss, whose first work concerned Loebian tropisms, arrived in 1931 to work with Harrison; in 1933 he moved to Chicago where he came under Child´s influence; in many respects he bridged their approaches. Hamburger arrived in 1932 and took up the chick as a research object. In some sense they (and the later arriving Spemann students) must have inhibited native Americans from intruding on their already well trodden areas of expertise). As regards Wolpert´s influence in the USA, PI featured for a time in US textbooks (and his work on the chick limb has continued to be prominently described), but it tended to be even more strongly represented in its derivative, Bryant´s "polar coordinate model" of positional information.