vances in Vertebrate Neuroethology, pp. 331–347. Eds J.-P. Ewert, R. R. Capranica and D. J. Ingle. Plenum, New York 1983.
13 Grobstein, P., On beyond neuronal specificity: problems in going from cells to networks and from networks to behavior, in: Advances in Neural and Behavioral Development, Vol. 3, pp. 1–58. Ed. P. G. Shinkman. Ablex, New Jersey 1988.
14 Grobstein, P., Between the retinotectal projection and directed movement: topography of a sensorimotor interface. Brain Behav. Evol. *31* (1988) 34–48.
15 Grobstein, P., Strategies for analyzing complex organization in the nervous system. I. Lesion experiments, the old rediscovered, in: Computational Neuroscience. Ed. E. Schwartz. MIT Press, Cambridge (1989) in press.
16 Grossberg, S., Communication, memory, and development, in: Progress in Theoretical Biology, Vol. 5, pp. 183–232. Eds R. Rosen and F. Snell. Academic Press, New York 1978.
17 Hamburger, V., The Heritage of Experimental Embryology. Oxford, New York 1988.
18 Holtfreter, J. F., A new look at Spemann's organizer, in: Developmental Biology, Vol. 5, pp. 127–153. Ed. L. W. Browder. Plenum, New York 1988.
19 Hebb, D. O., Organization of Behavior. John Wiley and Sons, New York 1949.
20 Hollyday, M., and Grobstein, P., Of limbs and eyes and neuronal connectivity, in: Studies in Developmental Neurobiology: Essays in Honor of Viktor Hamburger, pp. 188–217. Ed. W. M. Cowan. Oxford University Press, Oxford 1981.
21 Icardo, J. M., Heart anatomy and developmental biology. Experientia *44* (1988) 910–919.
22 James, W., Principles of Psychology. Holt, New York 1910.
23 Kauffman, S., Developmental logic and its evolution. Bio Essays *6* (1987) 82–87.
24 Kirby, M. L., Role of extracardiac factors in heart development. Experientia *44* (1988) 944–951.
25 Kohler, W., Gestalt Psychology. Liveright, New York 1929.
26 Lashley, K. S., Basic neural mechanisms in behavior. Psych. Rev. *37* (1930) 1–24.
27 Lloyd, S., and Pagels, H., Complexity as thermodynamic depth. preprint. (1988) Rockefeller University.
28 Lehky, S. R., and Sejnowski, T. J., Network model of shape-from-shading: neural function arises from both receptive and projective fields. Nature *333* (1988) 452–454.
29 Luria, A. R., Higher Cortical Functions in Man. Second Edition. Basic Books, New York 1980.
30 von der Malsburg, C., Ordered retinotectal projections and brain organization, in: Self-Organizing Systems. Ed. F. E. Yates. Plenum, New York 1987.
31 Maunsell, J. H. R., and Newsome, W. T., Visual processing in monkey extrastriate cortex. A. Rev. Neurosci. *10* (1987) 363–401.
32 McClelland, J. L., Rummelhart, D. E., and the PDP Research Group, Parallel Distributed Processing, Vol. 2. MIT Press, Cambridge 1986.
33 Moore-Ede, M. C., Sulzman, F. M., and Fuller, C. A., The Clocks that Time Us. Harvard University Press, Cambridge 1982.
34 Root-Bernstein, R. S., Setting the stage for discovery. Sciences *241* (1988) 26–34.
35 Rummelhart, D. E., McClelland, J. L., and the PDP Research Group, Parallel Distributed Processing, Vol. 1. MIT Press, Cambridge 1986.
36 Sperry, R. W., Chemoaffinity in the orderly growth of nerve fiber patterns and connections. Proc. natl Acad. Sci. USA *50* (1963) 703–710.
37 Sperry, R. W., Embryogenesis of behavioral nerve nets, in: Organogenesis, pp. 161–186. Eds R. L. Dehaan and H. Ursprung. Holt, Rinehart, and Winston, New York 1965.
38 Sperry, R. W., A modified concept of consciousness. Psych. Rev. *76* (1969) 532–536.
39 Sperry, R. W., The new mentalist paradigm and ultimate concern. Persp. biol. Med. 29 (1986) 413–422.
40 Udin, S. B., and Fawcett, J. W., Formation of topographic maps. A. Rev. Neurosci. *11* (1988) 289–328.
41 Waddington, C. H., The Strategy of the Genes. George Allen and Unwin, London 1957.
42 Weiss, P., The living system: determinism stratified, in: Beyond Reductionism, pp. 3–55. Eds A. Koestler and J. R. Smythies. MacMillan, New York 1970.
43 Wilson, E. B., The Cell in Development and Heredity, 3rd Edn. MacMillan, New York 1925.
44 Wolpert, L., Positional information and pattern formation. Curr. Top. devl Biol. *6* (1971) 183–224.

0014-4754/88/11-120960-12$1.50 + 0.20/0

Retrospection and prognostication: Ontogeny of a discipline

F. J. Manasek

Department of Anatomy, Dartmouth Medical School, Hanover (New Hampshire 03756, USA)

The present collection of papers concerning cardiac development approaches the field in a very catholic way, ranging from comparative anatomy and physiology to molecular studies. Perhaps as important as the data contained in them, these papers demonstrate very nicely how the problems of organ development and function can be viewed from many different vantage points. Moreover they provide a splendid overview that should enable workers in other fields to rapidly acquire a good insight into the field. In looking over this collection, I am impressed by the rapid rate of data accumulation, and I wonder about the ultimate direction in which the field is moving. What determines this direction? Is it dissatisfaction with pre-existing paradigms or is it an evolution brought about by new data that expands horizons? Certainly the relatively new work with neural crest has revised our perceptions of heart development. This is work that does not owe its existence to pre-existing models of heart development and it would be interesting to compare this work to others that have such a legacy. How do new data feed back to influence and modify their intellectual forebears? If the feedback operates slowly is this because of the inherent conservatism of the scientific process, the enormous inertia of the pre-existing mass of data compared to the mass of the new data or is it because some data are gathered and selected with pre-existing paradigms in mind and therefore tend to support that which is already known or thought to be known? These are some of the questions I will try to address in this essay.

This will be a very personal essay. I shall write about my insights into the field of cardiac development and the

strengths and weaknesses that I perceive to be resident in the body of investigative work that exists in this area and shall try to explore some aspects of the antecedent views that motivate it. I shall be concerned with views, inferences and the ways in which we draw these inferences from data, as well as the way inferences that we might wish to draw influence the subsequent accumulation and presentation of those data. My thoughts on this subject are the results of a long evolution; selective pressure being applied by stimulating discussion with many of my colleagues. In particular, regular conversations with Paul Grobstein over at least a year have shaped and focussed these views. One question should be raised immediately. Is it necessary or even proper to introduce a personal viewpoint into the science of cardiac development? In answer, we should note that personal viewpoints are already present and are inherent in the data. As long as the human machine either gathers data or interprets them, a degree of objectivity is lost. This is especially true in relatively new bodies of data. With time, as the information becomes distanced from its creators, it can become more independent of human bias. More recent data often carries with it an ecclesiastical momentum derived from the personality of the investigator. This momentum is often as important as the quality of the data. Secondly, I feel personally that we have reached an intellectual plateau in cardiac development and that for some reason the correct questions to ask are eluding us. Work of the past two or three years has not materially changed the way we think about the problems. This is not to say that there are no new data; indeed the field seems to have spawned a new generation of scientists; yet I have the uneasy feeling that some main issues are being skirted. We have a huge kettle of thought stew, which is certainly bubbling but which really does not satisfy the intellectual palate. I shall try, in this essay, to share these anxieties with my colleagues and perhaps open a new door for discussion. Perhaps at some time in the near future a critical synthesis of the existing body of work should be attempted. We may find it profitable to try to effect such a synthesis at a meeting where we can examine critically old data for new insight into old questions.

Cardiac embryology has a long history. However, instead of delving into ancient texts, such as those of Malpighi, which in the current context would serve only to add a scholarly veneer (since I cannot read them in their original) I shall begin with a recollection of a cardiac embryology meeting organized in 1968 by Oscar Jaffee. In retrospect, this meeting marked the transition of studies of heart development from the era of embryology to the era of analytical cell biology. It was probably one of the last times that some of the greats in the recent past of our intellectual heritage such as Bradley Patton and Ralph Shaner were able to present their works and it was both the first and last time that I heard them summarize their lifetimes of active work on the embryology of the heart. The succeeding two decades since this meeting have seen dramatic changes in the direction of work on the developing heart but have not diminished the fact that the pioneering work of these and many other cardiac embryologists still serve as the foundation of our current molecular and subcellular paradigms. It will be my attempt here to try to chronicle the change in the way we think about problems in cardiac development and to try to understand the forces that shape our thinking and how our perceptions of the question influence our acceptance of answers. I argue strongly that we need to perturb the ontogeny of thought, but we need to exercise care that such perturbations do not create malformations that result in conceptual cul-de-sacs.

Cardiac embryology does not exist in a vacuum. We can therefore make some fruitful comparisons to the way other scientific fields have responded to work done in them. One of my favorite examples is the work done in the 1830's by two German amateur astronomers, W. Beer and J. Mädler[2]. Using a relatively small refracting telescope, these amateurs produced a map of the moon's visible surface that far exceeded in accuracy anything done earlier. It was many scientific generations later until more significantly original selenographic work was done, perhaps because it was felt that Beer and Mädler's study was the definitive work and could not be improved upon. Moreover, Beer and Mädler concluded that the moon was devoid of change and this conclusion discouraged other workers from adding to the data. Most of the later work also employed critical parts of the Beer and Mädler map without significantly questioning them. Thus, by producing this beautiful map, Beer and Mädler may have actually induced a twilight of selenography while at the same time producing an important work. Another example worth mentioning is the more recent 'discovery' of polywater[5]. Polywater allegedly was a water polymer that formed when water was introduced into exceedingly small capillary tubes. The prestigious journal, Science, published many reports of polywater, its formation and characterization. There were even warnings about letting polywater out of the lab for fear that it would be a nucleus for the polymerization of all the world's water. It is easy, with the light of hindsight to suppose that for a time critical judgement had been suspended. But we must remember that polywater was so *plausable*! It is this kind of plausability that, we can argue, makes certain models, hypotheses and interpretations of data attractive and others less so. Geocentrism remained an attractive model even after it became encumbered with many layers of epicycles; the simpler and purer heliocentric model did not receive many votes in the scientific parliament. Certainly the Ptolemaic vision worked, had great heuristic value, and if some minor inconsistencies were ignored, there was no reason to seek another model. The Ptolemaic model had become so well worked out that when it reached its intellectual zenith in the 16th century, the difficult mathematical computations necessitating the use of the Rudolphine Tables of 1240 AD had been re-

placed with a set of analogue computers. That brilliant effort by Peter Apianus in 1540 resulted in the publication of one of the world's most beautiful astronomy books[1], but alas, Copernicus had already published. It was ultimately those annoying 'minor inconstancies' which would not go away that forced the introduction of an alternative model despite the fact that culturally, geocentrism probably made more 'sense'.

Embryonic development is a series of phenomena that result collectively in a continuum of morphologic changes characterized by the continual change of forms until the mature form is reached. At the cellular level, microscope examination of sectioned embryos of progressively later stages demonstrates that cells change also from one type ('undifferentiated') to another ('differentiated') becoming more like the mature form. The control of these changes and the mechanisms which initiate the decision making in each cell (why does a cell become muscle and not nerve, why does an epithelium change its organization to become mesenchymatous, etc) still remains unknown, but there are models that seem to fit the data and seem to offer a framework within which we can seek answers. However, are the answers to be found in that conceptual framework, or is that framework perhaps more analogous to geocentrism?

One of the most prevalent and influential concepts in development is that of induction. Induction is described as a phenomenon wherein one tissue (an inducer or inducing tissue) exerts an influence on another tissue causing it to change one or more of its characteristics; i.e., to differentiate. Many examples of induction have been repeatedly examined and studied. In this essay I shall restrict myself to comments on inductions thought to be involved in cardiogenesis. The most well known is the relationship between endoderm and the undifferentiated mesoderm. Precardiac mesoderm occupies a position rather close to the foregut endoderm. A series of experiments have suggested that the stimulus for the mesoderm to differentiate into cardiac muscle derives from the endoderm[4]. In other words, the endoderm 'induces' the expression of the cardiac muscle phenotyp. But does it really? What in principle should be a relatively easy test, i.e. growing 'uninduced' mesoderm in vitro with and without endoderm and monitoring the results is, in reality, quite difficult. One can never be quite certain that a tissue in vitro is a true analogue of itself in vivo. What does that act of explanting actually do to the cells? The tests we use to determine 'good cultures' are actually rather arbitrary and may not be what we should use. (If cells do what we want them to do, we consider the culture system to be a good one!) Further, temporal changes occur in the embryonic tissues even as they are acclimating to the new environment. And then we have to add the inducer tissue with all the caveats that were present for the first tissue. Only then can we begin to analyze the explants for response to the inducer. What constitutes a positive response? Certainly myofibrillogenesis and beating would be positive indication that the muscle phenotype is expressed. Invariably however, not all explants express the phenotype in the presence of the inducer and some of the explants lacking inducer (controls) differentiate anyway.

It is a useful thought experiment to pretend that we are not working within the induction paradigm and suppose that these studies were not done to 'demonstrate induction' but rather for some other purpose. If we did not already 'know' about induction, if induction were not already part of our biological culture and 'made sense', could the existence of an inductive phenomenon be deduced from this type of experiment? What should the criteria be? If the culture experiments are assumed to mimic in vitro phenomena should they do so quantitatively and temporally as well? Is induction a statistical event with, say 60% positives? Or does it occur in virtually all embryos? The induction paradigm would require us to argue that any differentiation that occurred in vitro in the absence of inducer could simply indicate that the mesoderm had 'seen' some induction before being explanted. Also, we can find reasons to ignore the failure of some of the recombined cultures to differentiate. In effect, this is to ignore the objectivity of the experiment and to selectively 'explain away' data that may refute the premise. We can also restrict our consideration to data of 'typical' experiments, while not considering those that 'did not work'. Once we do this, however, we can no longer judge the remaining data. In order for induction to be a meaningful biological phenomenon it should have to work in virtually all cases and we can argue that an experimental system that does not at least approximate the in vivo data is not sufficiently an analogue to use in testing the model. After all, insulin does not normally increase glucose uptake in 40% of all livers.

The argument assumes that we can actually determine the endpoint of differentiation, i.e. beating or fibrillogenesis. But can we really? In order to be practical about it, if we are setting up many cultures we may have to use a relatively fast and easy assay. As an example, the visual determination of beating or quiesence would be an adequate measure of muscle differentiation. However, can we really tell if any specific culture is beating? This is not a trivial question and I have personal experience in this area. I have spent many hours at the microscope trying to decide if very early hearts of explanted chick embryos are beating and many times I simply could not tell. In another example from my own laboratory, after months of working with the cardiac lethal mutant axolotl[4], I had not personally detected heartbeats. A medical student working in my lab, who did not 'know' that these hearts should not beat first made the observation that they indeed do. I prefer to use this not as an example of my careless science, but rather as an example of observer bias. This is one of the reasons why the double blind technique has been developed. I feel that many induction experiments have been set up (including some unpub-

lished ones in this laboratory) with the tacit intent of demonstrating the phenomenon rather than trying to falsify the hypothesis. Prior experience informs our view and makes neutrality difficult, at best. Any bias introduced by impartiality or failure to use a double blind can result in data being skewed unwittingly according to an investigator's bias. Certainly there can be no justification for truncating or censoring data. If a range of results are obtained then they should all be reported and not just those data selected that 'prove the point'.

'Mechanism' is a term that is used often in development. What does it mean? Does a mechanism have something unique and intrinsic to it that will permit us to identify it or is the recognition of a mechanism dependent upon the scientific climate in which the question is posed? The cardiac jelly, the large extracellular compartment between the endothelium and the myocardium of the early heart, is obviously a structural component of the heart. It is probably safe to suppose that a lack of synthesis of cardiac jelly would cause a major malformation of the tubular heart, hence this probably could be considered to be a possible mechanism of heart malformation. However, I know of no known recorded examples of spontaneous agenesis of cardiac jelly; indeed, it is unlikely that this would happen and if it did the embryo would not survive. The same would be true for myocardial agenesis. What about partial defects of synthesis? It has been shown experimentally that alterations of the cardiac jelly[6] alter the shape of the heart tube. Clearly there is cause and effect and many of these studies even have quite adequate control. Is this then a mechanism relevant to cardiac development? Would we first have to identify such a defect in a spontaneous malformation? Despite the more than 10 years since the reports that DON alters cushion development[6] the notion that this is an example of a mechanism of heart malformation has not obtained the status of becoming common knowledge. Is this because it is not a mechanism or is it because it is not perceived to be one? What will it take to have the scientific body politic grant acceptance? In other words, what are the criteria for something to be perceived as being a mechanism? I suspect that this cannot be answered because I think they have been trained to seek a global answer, in which a single developmental event is shown to be responsible for a complex entity and that identifying individual components of a multifactorial system is not good enough. Moreover, these events should also not be removed too far developmentally from their effect. Quite possibly we may never find a 'mechanism' because we cannot recognize it if it appears.

At lower levels we can expect to get more statistical uncertainty. It is quite possible that identifiable mechanisms involved in the regulation of complex organ shapes disappear as we search at lower levels of organization, and that as we trace events back to these lower levels of organization causality becomes lost in the fog of such statistical slack. However, this cannot be acceptable to an embryo which needs to have its mechanisms correct virtually 100% of the time. This also argues against the existence of a single mechanism being responsible for complex morphogenesis; rather it suggests a high level of redundancy and the existence of multiple causes, increasing hierarchically as lower levels of organization are approached, and each responsible for only a small amount of the final event. If the latter is true, then as we reduce the level of our investigations, many events we study may have only a small effect on the final product; an effect so small that a failure of the event would still be compatible with function and quite possibly not even detectable in an experimental system.

Earlier I argued that time may introduce a greater measure of objectivity to the evaluation of a set of data. Can we short-circuit this time? Perhaps we need to know where we have been and what we have before we make more. The traditional format of topical invitational meetings involves the sequential presentation of papers reporting individual investigators' latest research. Questions and answers follow and the cycle repeats. Would it not be profitable to change this format, put the old wine into new bottles and reassess the problems of cardiac development and try to formulate the problems in a context amenable to the newer research techniques?

Acknowledgement. The author thanks Dr David Hanlon for critical comments. Support: HL 37703.

1 Apianus, P., Astronomicum Caesareum. (Author's Press) Ingoldstadt 1540.
2 Beer, W., and Mädler, J. H., Mappa Selenographica totum Lunae Hemisphaeram visibilem. Simon Schropp & Soc., Berlin 1834.
3 Humphrey, R. R., A genetically determined absence of heart function in embryos of the Mexican axolotl (*Ambystoma mexicanum*). Anat. Rec. *162* (1968) 475.
4 Jacobson, A. G., and Duncan, J. T., Heart induction in salamanders. J. exp. Zool. *167* (1968) 79.
5 Lippincott, R., Stromberg, R. R., Grant, W. H., and Cessac, G. L., Polywater. Science *164* (1969) 1487.
6 Markwald, R. R., and Bernanke, D. H., Structural analysis of 6-diazo-5'-oxo-L-norleucine effects upon early cushion tissue morphogenesis, in: Perspectives in Cardiovascular Research, vol. 5, pp. 237–251. Ed. T. Pexieder. Raven Press, New York 1981.

0014-4754/88/11-120971-04$1.50 + 0.20/0