From the head to the heart: Some thoughts on similarities between brain function and morphogenesis, and on their significance for research methodology and biological theory

PAUL GROBSTEIN

DEPARTMENT OF BIOLOGY

BRYN MAWR COLLEGE

BRYN MAWR, PENNSYLVANIA 19010

(610) 526-5098 pgrobste@brynmawr.edu

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Summary. A broad review of the phenomena of morphogenesis and of brain function, and of the history of research in these two areas, suggests that there are quite striking similarities between the two sets of biological phenomena. Among other things, both reflect the interaction of internally complex components at several levels of organization, display variance as an essential characteristic, and incorporate information from the environment. It is argued that reductionist approaches are inadequate to deal with fundamental problems of either morphogenesis or brain function, and alternative foundations for research strategy and tactics are discussed. Attention is also given to the question of why morphogenesis and brain function are so similar, and it is suggested that this may reflect the existence of rules of information acquisition. transmission, and storage to which both are subject. Variance, it is argued, is an essential component of information acquisition processes, and hence of biological integrity, at all levels of organization.

"Poems are made by fools like me, but only God can make a tree." - Joyce Kilmer

Trees do present an interesting problem though from some significant points of view no more so than poems. One can, of course, make a tree without being God. It is easy enough to plant a seed and wait for a tree to emerge. This does, however, miss the point a bit, since one is not so much making a tree as allowing one to happen. Alternatively, one could construct some kind of an image of a tree. Painters and set-designers construct such images, with remarkable success, but there is an important characteristic missing in this case: the capacity to change with time. Indeed, among the most remarkable things about a tree is that it does change with time. Still more remark able is that it remains a tree despite those changes.

The phenomenon is of course not unique to trees. Humans remain not only humans but individually identifiable humans despite the enormous changes which occur as they grow, mature, and age. Two conclusions follow from these sorts of considerations. The more obvious is that the processes underlying the form of living organisms are such as to permit substantial differences in detail while maintaining some kind of more general invariance. What may be less obvious, but is no less significant, is the conclusion that the human brain is organized so as to be able to detect such invariances despite the same quite significant differences in detail.

'Treeness' is clearly a relevant property when talking about either morphogenesis or brain function, and in both contexts has a similarly abstract character. This is by no means the only common ground in considering the two. Such distinguished scientists as Paul Weiss (42) and Roger Sperry (37, 38) have been attracted to both areas. Both fields have seen major struggles over similar concepts, the 'localization' problem providing perhaps the most dramatic example (compare, for example, Chapter XIV, Section 11, in Wilson (43) and Chapter 1 in Luria (29); see also recent discussions of the history of research on the organizer (l7, 18). Similar computational formalisms are increasingly being applied to both (16, 30). The range of similarities extends further still, and is striking enough to suggest that, at some deep level, morphogenesis and brain function represent quite similar problems. In this article, I want to discuss some of the common characteristics in studies of morphogenesis and of brain function. My objective is not only to call attention to experiences in one field which may be helpful in the other but, more generally, to suggest a possible explanation to the intriguing question of why two apparently so different natural phenomena should be so similar.

Bounded variance

To the brain, a tree is clearly not a particular constellation of attributes but rather some kind of relation among a number of attributes each of which can itself vary over a rather wide range. It is of considerable interest that this reality was not only well documented but served as a theoretical and methodological starting point for gestalt psychology (25), and yet was until recently largely ignored by all but a relatively small number of investigators inter ested in brain function (11, 19, 26). Part at least of the problem was that the metaphors dominating brain research were for an extended period those of physics during the early machine age: the needle on a device consisting of cogs and gears can reasonably be expected to point to ward the word 'tree' if and only if each of a series of cogs and gears is in an appropriate position. If one regards a tree as a collection of attributes and those in turn as setting the positions of the cogs and gears at some low level of the machine, one would need an enormously large and complexly interconnected set of elements to have the needle point correctly to 'tree' for all of the various collections of attributes which a given brain so designates, but such a machine could in principle be built. From this perspective, what seems relevant is the me chanical question of how the cogs and gears are interconnected rather than two potentially more productive questions. Is this actually the general way the brain recognizes things? And perhaps even more importantly, why is the system built to tolerate such variability?

There are a variety of reasons to think that the answer to the first question is no: the machine metaphor does not provide a good reflection for the brain processes underlying recognition (10, 28-31) One is particularly germane here and others will be treated in following sections. A machine of the sort

described would correctly identify as tree all those various constellations of attributes which it has been built to identify. Others, however, will give it trouble. Here the morphogenetic problem becomes relevant. For the brain in its machine-like incarnation to repeatedly identify a tree as a tree, or a particular human as a particular human, despite the changes each under goes with time, one would have to presume not only an enormous complexity of the cogs and wheels, but a relation between the morphogenetic process and the brain process underlying recognition which assures that the variance associated with the former is sufficiently predictable so that it remains within the limits of the repertoire built into the latter. Despite the complications, this line of thinking has an appealing corollary which might make it superficially entertainable: perhaps the reason why the recognition system is built to tolerate variability is that variability is inherent in the morphogenetic processes which create the things which the brain needs to be able to recognize. The problem with this argument is threefold. First, it simply defaults the question of why the brain is built to tolerate variability to the question of why there is variability in the morphogenetic process. Second, a lot of what brains identify as trees never appears in nature. Third, it provides no explanation for the fact that persistance of general form despite local variance seems to be a general property of the nervous system, rather than one specific to the recognition function. The same phenomenon is equally evident on the output side of the nervous system, where it is usually termed 'motor equivalence'. The trajectories of even simple skilled movements performed by a single individual all accomplish the same objective but vary substantially from instance to instance (2).

Two points follow from this. The first is that what I will call bounded variance' seems to be a common property of both brain function and morphogenesis, without their being any obvious causal relationship between the same phenomenon in the two sorts of processes. This not only establishes a point of similarity between the two but suggests that the reality of variance, and the issue of why it exists, should perhaps be regarded as primary rather than secondary in studies of both brain function and morphogenesis (4). In both fields, there has been some tendency for investigators to presume that a complex process is designed' to have a particular, single, and well-de-fined outcome, and hence to search for some equivalent of a cog and wheel machine which yields that outcome for particular inputs and starting conditions. As discussed in the following section, this can cause problems if what is being explored is a situation of bounded variance.

Multiple mechanisms, the levels of organization problem, and experience dependance

An instructive example with regard to both the problems of the cog and wheel approach and with respect to some additional similarities between morphogenesis and brain function is a large and contentious literature bearing on perhaps the most challenging form of the morphogenetic problem, accounting for the genesis of highly ordered patterns of connectivity among neurons. The stimulus for this literature was what came to be called the chemoaffinity hypothesis (36). Borrowing from earlier work on morphogenesis in sponges, Roger Sperry proposed that the patterning of neuronal networks reflected processes of cellular individuation and recognition enormously more refined than but in principle the same as those underlying specific aggregation of sponge cells. What followed from this was an extended period in which investigators reported a variety of experimental observations both consistent and inconsistent with the notion that neurons would form synapses only at locations corresponding to their targets. The inconsistent observations led to alternate hypotheses to account for the genesis of neuronal networks, and to still further publications aimed at establishing that deviant observations were actually

consistent with one or another of the competing hypotheses. It was not until about 1980 that investigators began to entertain the idea that the various hypotheses were not mutually exclusive that the phenomena being studied were in fact sufficiently complex so that under one set of experimental conditions observations would be dominated by specific aggregation effects, and under other conditions by other factors also normally involved in the patterning of neuronal circuits (13, 20). Similar histories in which different groups of investigators develop evidence for different machines, there is a period of dispute characterized by efforts of each group to prove the others wrong, and it is ultimately realized that several machines are in fact operating have characterized not only other areas of morphogenesis but of research on brain function as well (Grobstein (15) for some neurobiological examples).

With regard to at least a portion of the literature on the genesis of neuronal connectivity, an important element in the ultimate acceptance of the existence of several different morphogenetic mechanisms, each of which could by itself lead to a more or less normal' outcome, was the recognition that the normal developmental process does not in fact have a fixed and stereotyped outcome. The topographically organized retinotectal projection in fish and amphibians. the battleground for much of the struggle over the chemoaffinity hypothesis, turned out to represent a noteworthy example of 'bounded variance'. As with a tree, what is constant is actually not detailed organization among a set of elements which make up a pattern but instead an abstraction evident only at a higher level of organization. The retinotectal projection always relates retinal to tectal regions in a way which preserves neighbor relations and overall map orientation. At the same time, the particular tectal region to which particular retinal regions project varies with growth in normally developing animals (40). A reasonable interpretation of the dependence of the projection on several different mechanisms is that the combination assures not only global order at any given time but an ability to produce the kind of local variance needed to maintain global order under changing conditions (13, 20).

Recognition that the problem is accounting for bounded variance and that this in turn typically involves several interacting mechanisms (what I have termed an 'adaptive developmental program' (13)) is not only significant in its own right, but also helps to clarify the relation between properties at different levels of organization, a persistant point of concern in studies of morphogenesis (and of brain function as well (15)). The chemoaffinity hypothesis, in its strictest form, suggested that an orderly pattern evident at one level of organization (topographic mapping in the retinotectal projection) reflected a comparable orderly pattern at a lower level of organization (the recognition characteristics of individual neurons). The hypothesis is an example of 'naive reductionism' (13), the presumption that there exists a single set of properties at a lower level of organization which suffices to account for those at a higher. In fact, the recognition process involved in retinotectal patterning is less precise than is the mapping: it permits connections at locations in addition to those found in a given normal map (3). This is of course desirable to permit variations in the map. The relevant point here, however, is that when one is dealing with situations of bounded variance, 'naive reductionism' is generally a poor starting point. Order at one level of organization is unlikely to reflect a corresponding order in some property of elements at a lower level of organization. It instead generally reflects an interaction of several sets of lower order properties.

There is an additional point worth making in this context, which relates to reductionism more generally. The argument is frequently made that more complex systems can only be understood in terms of the properties of the elements making them up, and that a catalogue of the latter necessarily suffices to

account for the properties of the former. There are a variety of reasons to be skeptical of such assertions (13). Among them is the somewhat imprecise intuition that "The whole is more than the sum of the parts"(42). This intuition can be made more explicit from the perspective of adaptive developmental programs. These programs are frequently organized so as to involve repeated additions of information as development proceeds (13). In the retinotectal case, for example, the recognition characteristics of neurons are apparently established by events occurring quite early in development. Other mechanisms acting at following points in time adjust the connection pattern based on the size of the cellular populations. In short, the pattern seen at the higher level of organization is genuinely more than the sum of its parts in the sense that it reflects an addition of information subsequent to that involved in determining the properties of the elements which make it up. In such cases, it is not only naive reductionism but reductionism itself which needs to be taken with a grain of salt. It is only in rare cases that form will appear spontaneously when one mixes an array of elements. Much more common is that form depends not only on the elements but the history of their interactions with each other and with external factors. What the properties of elements do is to constrain the possible forms of higher order organization which can exist. What they almost never do is to constrain them to the particular form observed; this constraint is the business of additional information (see Anderson and Wenink (4) and Icardo (21) for evidence on this point in the context of cardiac morphogenesis).

I have recently argued that bounded variance, and a corresponding dependence of morphogenesis on an adaptive developmental program rather than a single cellular mechanism, is a fairly general characteristic of nervous system development (13). Experience with the heart is not such as to suggest that it is substantially more rigid than the brain (6, 21, 24,). Indeed, it seems to me unlikely that brain morphogenesis differs greatly from morphogenetic processes in general, suggesting that the principles of an adaptive developmental program almost certainly have wider relevance. What is additionally interesting in the context of this article is that similar principles seem to hold for brain function as well (13, 15). A given input output relationship, for example, it not fully determined by the anatomical structure of a neural network. The network instead, in general, permits an array of input output relations with the particular output depending on additional factors; typically factors which provide information over and above that inherent in the network. Here too, specificity at a higher level of organization (behavior) reflects an interaction of several less-specific processes at a lower. Here also, addition of information is generally important in linking between lower and higher levels of organization. In short, a particular kind of relation between higher and lower order properties, one in which the latter do not follow directly from the former, is an additional similarity between morphogenesis and brain function, one which like 'bounded variance' needs to be taken into account in the strategy and tactics of experimentation in both areas (see below), and one which further implies a deep underlying isomorphism between the two sets of phenomena.

Autonomy, self-regulation, the localization problem, and distributed function

While the similarities between morphogenesis and brain function outlined to this point seem to me significant and instructive, they are actually neither the most striking similarities nor the ones most frequently remarked on in the literature. "Many lines of evidence show a close parallelism between the facts of morphogenesis and those of the organization of the nervous system. In both we have given as the fundamental fact an organization which is relatively independent of the particular units of structure and

dependent on the relationship among the parts. In both there is a capacity for spontaneous adjustment after injury, so that the main lines of organization are restored; in both there is evidence that a part may influence every other; in both there is a possibility of dissociation and independent activity of some parts." (26) Lashley's last three points summarize the more dramatic parallels between morphogenesis and brain function: the evidence, largely from lesion studies, that both morphogenesis and brain function have an integrity which often appears disturbingly free of their material substrates.

What has been similar in studies of morphogenesis and of brain function is not only the experimental facts but the responses of investigators to those facts. The vitalism/mechanism controversy in developmental biology bears close similarities to the mind/brain issue in brain research. In both cases, there have been quite significant investigators for whom the evidence seemed to compel the presumption that there must exist some organizing force independent of the material substrates under investigation. In both there has been an even more vigorous counter-reaction, one which not only defends materialism but does so so strongly as to confuse it with one or another form of reductionism. Characteristic of the latter is an assertion that questions can be meaningfully asked or answered only at some low level of organization, typically for both morphogenesis and brain research, the cell and increasingly the molecule. Phenomena which seem not explorable at that level are laid aside, and investigators who persist in reminding others that they exist are ignored, usually with some feeling that the offenders can not possibly come up with meaningful answers to the problems they raise, and are probably closet spiritualists anyhow. What is at issue here is a domination of thinking by not only the cog and gear paradigm of machine age physics but the deeper logical posture of late nineteenth and early twentieth century philosophy: the way to approach reality is to get the postulates and laws of inference right, after which everything else follows as a demonstrable theorem. Working biologists tend to be oblivious to the fact that both physics and philosophy have moved beyond their earlier realities. One could know all of the properties of physical elements at any known level of scale and still not account for reality without knowing how the elements are organized in relation to one another at some point in time, a feature which physicists still cannot account for in terms of the properties of the elements (1, 8). Within any well-defined logical system, there exist true theorems which cannot be proven given axioms and principles of inference (7). Far from spelling the end of either physics or philosophy, these realizations have been a significant source of reinvigoration of both disciplines.

In this context, it pays to briefly review the disturbing features of both morphogenesis and of brain function, not only to establish their further similarities, but also to show that they can be dealt with, in similar ways, without recourse to the spiritual. At the most general level, morphogenesis and brain function are similar in that both involve changes in the state of semi-closed systems each of which has, at any given time, a substantial internal organization. By semi-closed I mean that one can, with some adequate degree of precision, define the boundary of the system, with the boundary being of such a kind as to permit transfer of matter, energy, or information between the environment and the system under study. Because of such possibilities of transfer, both systems may respond to environmental changes with changes in internal organization. Such changes may be visible from outside the boundary but need not be. At the same time, because of the internal organization, both systems may change their internal state in the absence of changes in the environment. These changes too may be either overt or cryptic. Given the latter, responses of the system to changes in the environment may in both cases be quite variable or apparently unpredictable.

None of the preceding ought to be surprising to either morphogeneticists or brain scientists. At the same time, the former are perhaps generally more used to the idea of internally generated changes of state, and the latter to the idea of externally generated ones, so it pays at least to note for each the relevance of what may seem obvious to the other. It also pays to make explicit that one can acknowledge in both systems a substantial autonomy, in the sense that each may change without changes in the environment, without appeal to the spiritual. It would suffice to presume that the machines underlying morphogenesis and brain function each have some kind of internal clock, a structure which can certainly exist as a material object (and does in virtually all biological systems (33)). Other forms of endogenous change can be imagined equally well (an internal waterfall, for example), but a clock serves as an adequate metaphor for present purposes. There is furthermore no difficulty in imagining that this material clock-like function possesses material linkages which alter internal organization in such a way as to produce internal changes in state and consequent alterations in response to environmental variations.

An initially somewhat more mysterious aspect of the autonomy of both morphogenesis and brain function has to do with the relation between the entirety of a system and its parts. One can readily put a cog and wheel clock into a cog and wheel machine with the result that all parts of the machine will behave in a coordinated way. What is a little distressing however, from this perspective, is the notion that one can nearly arbitrarily disassemble the machine and pieces of it will continue to display autonomous functions not dissimilar from those of the whole. This serves as a not unreasonable metaphor for regulatory phenomena in both morphogenesis and brain function, and is, in fact, quite explicitly the case for time keeping phenomena related to the latter (33). Parts behaving like wholes certainly sometimes inspire both awe and denial but it too can be dealt with without appeal to the spiritual. If a material clock-like function can be imagined for the system as a whole, it can also be imagined for any (or all) parts of the system. This suffices to account for the behavior of isolated parts but leaves one with the problem of overall coordination in the whole. This problem too can be handled materially if one accepts that each part is in fact, like the whole, a semi-isolated system with an autonomous organization and a boundary across which it can exchange information with other semi-isolated systems. This too is a good metaphor for many morphogenetic and brain phenomena and is explicitly true for time-keeping functions. Temporal coordination in nervous system function is due not to a master clock but to a large number of differently located clocks and information exchange pathways by which they entrain one another (33).

This picture of material reality sheds additional light on the level of organization problem mentioned earlier. If one is interested in time-keeping, one can certainly isolate any one of the parts of the system under investigation which also displays a time-keeping function and reduce it to characterize the mechanical basis of its time-keeping function at increasingly cellular and molecular levels. In doing so, however, it is important to keep in mind that one is no longer exploring the problem of time-keeping by the system as a whole. Critical aspects of that phenomenon have disappeared in the reduction: the problem of how different clocks are coordinated with one another. Those phenomena exist only at a higher level of organization and can be studied only at levels where they continue to exist. The hazard of an unthinking reductionism is not only that important phenomena are ignored but further that the isolated part itself may be misunderstood or appear unnecessarily complex. An element not only keeps time but normally does so by exchanging information with other elements and its internal organization must reflect this. The behavior of the isolated system is, under normal circumstances, determined not only by

its own organization as characterized in isolation but also by additional information which it receives at subsequent points in time from other semi-autonomous systems with which it communicates.

To this stage of the argument, what we have reached, without spiritualism, is a picture of both brain function and morphogenesis as the behavior of an array of inter-connected semi-autonomous parts. In consequence, there is no necessary fixed relation between the behavior of any part and the behavior of any other part, as there is in a cog and wheel device, nor is there any necessary fixed relation between the behavior of any part and the behavior of the whole. That is not, however, to say that overall behavior is not a function of the parts or that different parts may not have different internal organizations There may well be differences between different parts of the machine, demonstrable by isolating the parts or in other ways (15), but the differences bear no simple relation to different aspects of the function when one views the machine as a whole. What is localized in a developing embryo is not parts of an adult organism, but an array of systems which interact to yield one. What is localized in an adult brain is neither poetic skill nor audacity but rather interacting systems which may yield either or both in the function of the system as a whole. Both morphogenesis and brain function behave to a significant extent as parallel, distributed information processors, a kind of device which is of increasing interest to computer scientists and which they have become increasingly sophisticated at characterizing (32, 35).

Common to both morphogenesis and brain function is not only autonomy but also purposiveness, in the sense of an ability to respond in compensatory ways to externally imposed disturbances. Like autonomy in its simplest sense purposiveness in this sense clearly does not require a belief in the spiritual. A fully material object, a thermostat, is capable of endowing our machines with a compensatory response. As with the clock, the thermostat serves as an adequate metaphor for a larger ensemble of material objects: any of those which monitor some variable in comparison to a set point and which can cause internal changes of state so as to return the variable toward the set point. Also as with autonomy, however, purposiveness displays some more troubling characteristics. Both morphogenesis and brain function exhibit some rather remarkable abilities to sustain global function despite not only major changes in the environment but major disturbances in their own organization. It is the latter, particularly, which inclines some to wonder whether an understanding of the behavior of these systems does not require some non-material organizing principle, something which sustains an ideal image of the function of the whole which serves to reorganize its components in the face of insult.

One might, of course, argue that there is no reason to be surprised at the homeostatic capabilities of either morphogenesis or brain function, that the underlying machines have been constructed on the basis of experience with all possible insults, or at least with those for which they seem capable of compensating. This, however, is a bit like associationism in psychology: the presumption that complex organization is based entirely on experiences with the environment. James (22) argued cogently (see also Goldstein (11)) that experience with the environment is really not so regular as to yield the kinds of thought associations which characterize the human mind (as in the identification of 'treeness'), and it seems equally unlikely that the environment has been sufficiently regularly challenging to account on this basis for the magnitude and details of the observed compensatory processes in either morphogenesis or brain function. A designer, of course, might well note the need for a compensatory response to certain deviations, take a thermostat from the shelf, and discover that that particular thermostat maintains homeostasis over a range of deviations wider than those which provoked the action. Even this, however, does not provide a good

feeling for how either brain function or morphogenesis can maintain global function not only in the face of major environmental perturbations but also despite destruction of significant parts of the material structures on which each is based. The latter frequently involves organized changes in remaining structures, changes which themselves have a purposive character.

Two additional factors seem to play a role in these more extreme expressions of homeostatic behavior, both also accountable for without appeal to the spiritual. The first is that, as with the clock-like function, a homeostatic function is a property not of a single isolatable part of the system but rather of a large number of the semi-isolated parts which make it up, and these communicate with one another to yield the homeostatic characteristics observed at a higher level of organization. Auto-pilots frequently consist of redundant sub-systems to assure appropriate function despite failure of or disturbance of individual components. More subtlely, the degree of success that one sub-system has at maintaining homeostasis can serve as an input to another sub-system, changing its set point and hence the role it plays in assuring homeostasis at a higher level.

A substantial degree of compensatory behavior could exist simply as a consequence of information exchange between semi-isolated components at a given level of organization. At the same time, there is good reason to suspect that both morphogenesis and brain function reflect an important additional organizational feature: top-down' regulation (38, 39). An arrangement of components at any given level of organization can create at the next higher level of organization a new semi-isolated system which has its own autonomous and homeostatic properties. If the latter receives both its own input from the environment and input from lower level components, and can act on those components, it will exert an additional and distinct organizing effect. The behavior of a given cell in heart morphogenesis, for example, may be influenced not only by other heart cells but also by blood pressure, which is itself a function of the behavior of the heart as a whole, and which may be both detected and communicated as such by organized groups of cells (24). Similarly, the behavior of neurons responsible for generating the orderly motoneuron discharges underlying locomotion reflect not only their own properties but inputs from higher order systems which monitor both the function of the premotor neurons and the effects of those activities on the function of the organism at higher levels of organization. Self-conscious' behavior seems to reflect perhaps the most well-developed top-down regulatory function known: a particular ensemble of neurons having its own homeostatic and clock-like functions, probably the neocortex, receives fairly direct information from the environment as well as information about other similarly endowed cell ensembles and is capable of acting on them to cause coordinated behaviors other than those which the ensembles would exhibit by themselves.

In the present context, a particularly noteworthy characteristic of top-down regulatory processes is that their function does not depend on the production of any particular array of states in the regulated lower-level components. The controlling variable in the homeostatic organization of the higher order system is itself an abstraction, one which might in principle be served by any of a number of arrangements of the components. This is of obvious interest in connection with the phenomenon of 'bounded variance', but has a deeper significance as well. If lower level components possess not only clock-like and homeostatic functions but also some dice-throwing device, then the system as a whole becomes a mechanism for exploring alternative solutions to problems presented to the overall system. Add a mechanism for storing information about the efficacy of solutions, and one has a learning machine.

Of still greater interest is that if homeostasis is a distributed responsibility of systems at all levels of organization, then a dice-throwing characteristic can be permitted at all levels including the highest. If lower level systems and their interactions suffice for maintenance of homeostasis under many circumstances, then under those circumstances the system can afford the luxury of exploring novelty for its own sake rather than in an immediate problem solving context. Not all of life is a matter of solving life-threatening problems, morphogenetic or otherwise. There are times when one can afford the reverie needed to write poems. There are also long-term benefits to be gained by doing so, as I will argue further below.

A machine consisting of several levels of organization of interacting semi-isolated systems, each having an internal organization creating clock-like, homeostatic, and dice throwing functions, is a quite different beast from the cog and gear machine with which I started this essay. Most importantly, it is a material object which can nonetheless be reasonably expected to display most of the characteristics of both brain function and morphogenesis which incline some to argue imply the existence of a spiritual component, and others prefer to forget as important parts of the reality of both kinds of processes. The machines are thus analyzable but, as I will argue in the following section, such analyses cannot effectively proceed without recognizing the similar complexities inherent in both morphogenesis and brain function. In the final section, I will take on the question of why these complexities, together with those characteristics discussed earlier, are similar in the two superficially quite different situations, and what further implications this has not only for studies of morphogenesis and brain function but for studies of biological organization generally.

Implications for research strategy and tactics

I have recently made this point in the context of neurobiology (15), and the argument seems to me directly transferable: it is simply not the case that an analysis of the properties of cells or molecules (or any lower level element), no matter how complete, will provide anything close to an adequate understanding of either brain function or morphogenesis. Both processes reflect, at several different levels of organization, associations of elements in ways not fully determined by the properties of the elements themselves. These associations frequently reflect addition of information subsequent to that which determines the properties of the individual elements; they can be influenced by other associations at the same level of organization as well as by higher level organizational elements. In short, the properties of an isolated element may not only bear little relation to the functional characteristics of the ensemble of which it is a part but may also be quite different from those of that element in the over all context. The myth that analysis at finer and finer levels of detail is the objective of studies of morphogenesis and brain function has been effectively driving research for a long time. Is there something which can effectively replace it? Are the phenomena to which I have drawn attention useful in motivating research, or does what I have outlined represent simply an acknowledgement of complexity from which nothing follows but discouragement ?

I have elsewhere argued, in the context of brain research, that the appearance of discouraging complexity is largely a function not of the phenomena of brain processes themselves, but rather of a perspective on such phenomena which anticipates an explanation of them by studies at the molecular and cellular level (15). This has not come to pass, and will not, either in the case of brain function or that of morphogenesis,

for reasons discussed in this essay: there are too many levels of organization, each with their own characteristics, intervening between the lower levels and the organismal level at which the phenomena of initial interest are displayed. The analysis of many of the phenomena is a good deal less formidable when defined in terms of questions posed at a level of organization closer to that at which they appear. While the search for molecules underlying cellular recognition goes on, it was fully possible, for example, to resolve in the interim the at least equally interesting issues of whether some kind of recognition process exists and whether it provides the full explanation of retinotectal patterning. Examples of this kind can be multiplied ad infinitum for both brain research (15) and the analysis of morphogenesis (44). They ought to serve as adequate evidence that meaningful questions can be posed and answered at levels above the cellular and molecular.

If the problem is not to characterize the cellular or molecular basis of one or another phenomenon, the issue, of course, is what is the task in studies of either morphogenesis or brain function? Most generally, the present discussion implies that what is needed in both cases is to identify the involved semi-isolated systems at various levels of organization and to characterize the interactions among them. In short, a minimum requirement for the continued successful analysis of both morphogenesis and brain function is a renewed interest in, and encouragement for research at a variety of different levels of organization. A further implication is that the 'simple system' approach to both nervous system function and morphogenesis can be overdone. It is possible to find situations in which properties at a higher level of organization do bear some close resemblence to the properties of elements at a lower level: sponge cells will exhibit species-specific aggregation, and mosaic development does occur in some organisms. The risk, however, of looking for and focusing on situations of this kind, is that one ends up seeing what is to be expected from lower order properties, and is accordingly not only failing to discover more interesting properties but being misled about the generalities of both morphogenesis and brain function. What really needs study is not the simple but the manageable: situations in which the components of a system seem enumerable and manipulatable but the output appears difficult to understand in terms of them (12,14). It is in these sorts of situations that one can hope to discover not only new elements and new properties of elements but also come to new understandings about how elements interact with one another. From this perspective, not form per se but changing form, as in growing trees, adapting hearts (21, 24), or the metamorphic phenomena so ubiquitous among living organisms (13), would seem to be a particularly promising area of study.

Acknowledgement of the complexities of both morphogenesis and brain function also encourages a productive renewed attention to matters of experimental tactics and the logic by which inferences from experimental observations can and cannot be drawn (15). So long as one expected phenomena at one level of organization to be accounted for in terms of elements with similar properties at a lower level, it was possible to ignore the in fact quite difficult and quite important questions of how one knew what to look for at the lower level, and whether observations made actually established the causal significance of lower level properties for higher level phenomena. In the retinotectal case, for example, what was early established was that cell recognition processes were adequate to produce a topographic mapping. The experiments were never, however, of such a kind as to prove that in normal development they were necessary for this form of morphogenesis. Indeed, it is not at all clear that a demonstration of causal necessity in this sense is an appropriate criterion for success in studies of either morphogenesis or brain function (15). Characteristically, one attempts to establish the necessity of a given lower order property

for a particular higher order phenomenon by showing that the higher order phenomenon disappears when the lower order property is disturbed. Such 'lesion' experiments are, however, always subject to the reservation that there exists some unknown property also normally adequate to produce the higher order phenomenon but whose expression is blocked by disturbance of the chosen lower order property. An alternate approach to establishing the necessity of one property would be to try and show the inadequacy of all other conceivable lower order properties to produce that phenomenon. This, however, also runs into the problem of the potential existence of unknown properties.

The difficulty here is neither semantic nor trivial, nor is it a consequence of a misguided concern for the complex. The apparent reduction of higher order phenomena to cells and molecules provided a spurious sense of rigor in experimental analysis, one logically no more defensible than that used for appropriate sorts of observations at other levels of organization. Demonstrations of causal necessity of either of the sorts discussed depend on working with closed systems, systems in which the possible causes of a particular phenomenon are enumerable in advance. The history of research on both morphogenesis and brain function is clearly such as to indicate that one is not working, at any level of organization, with closed systems in that sense. Indeed, the likelihood is that any given phenomenon does have multiple causes, including ones unsuspected by investigators, and that these do interact with each other in unknown and complex ways. This not only makes useless a number of formal rules of logical inference (e.g. A or B. not B, hence A) but implies that such informal ones as Occam's Razor are likely to be misleading. The simplest answer is rarely the correct one. What all this indicates is that one needs for the analysis of both morphogenesis and brain function some criterion of success other than the demonstration of causal necessity. In fact, morphogenesis and brain function are by no means unique in this regard: they simply call dramatic attention to a problem common to most areas of science. Like them, the analysis of both morphogenesis and brain function actually proceeds not by way of observations proving that something is so, but rather by ones proving that something is not so and hence establishing the existence of some causal factor or interrelation of factors not previously suspected to exist. No matter how elegant, it has never been studies establishing causal relations with in the limits of some reasonable application of Occam's Razor which move science along. It has instead been those which establish the existence of some unknown factor or interaction of factors whose properties then become the subject of further inquiry.

The method of advance by hypothesis and disproof, rather than hypothesis and proof, may seem odd to many scientists, but it has both a number of advantages and a proven track record. Among other things, the method is generally applicable and effectively self-correcting. One can take a phenomenon at any level of organization and construct to account for it an hypothesis, in terms of semi-closed systems at a lower level of organization, which yields predictable outcomes under some novel set of circumstances. The failure of those predictions then provides evidence from which one can construct new hypotheses about the lower level elements and their interactions, and so on and so forth. One can also freely move among levels of organization, since the findings at one level both motivate hypotheses about likely interactions at a lower level and suggest new ways to account for properties at a higher. In short, one can actually quite comfortably do away not only with the presumption that one is dealing with logically closed systems, but the presumption that there is some most fundamental level of explanation as well. That this agnostic approach works ought not to be surprising, since it is in fact the way humans first make sense of the world, and the way most humans continue to do so in their day-to-day lives. Children make no presumption either that there are an inevitably fixed number of alternative explanations for a given

phenomenon or that there exist basic building blocks of reality. They instead imagine and play, constructing and destroying hypotheses at all levels of organization based on their day-to-day interactions with the world.

Scientists, at their best, do the same, with the exception that the observations are more deliberate and specialized, and that a step of communication and social validation has been recognized to be helpful in the whole process. The task is and has always been to try and make better and better sense of the world: not to establish truth but to create hypotheses which effectively summarize wider and wider sets of observations. The creative side of science is and always has been as important as its concern with standards of demonstration and logical inference (34). As discussed below, what this implies is that variance is almost certainly a fundamental part not only of morphogenesis and of brain function, but of the scientific enterprise itself, one which needs to be not only acknowledged but encouraged.

Morphogenesis and brain function: why so similar and why care?

The starting point for most analyses of morphogenetic processes is the presumption that what is to be accounted for is an organization which elaborates over time a particular form. The starting point for most analyses of brain function is the presumption that what is to be accounted for is an organization which establishes particular relations between an organism and its environment. From this perspective, there is no obvious reason why there should be the kinds of similarities in the underlying organizations which there appear to be: one is responsible for bringing a form into existence and the other governs the function of an existing form. Nor, for that matter, is there any obvious explanation for why either should have the rather complex character they seem to share. If one were to hand one engineer the problem of elaborating a large tree out of a small seed and a second the problem of designing a device which behaves in particular ways in relation to the environment, one would expect solutions to the assigned tasks which not only differ from one another but are both a good deal simpler than what has emerged from studies of the related biological systems. One would also expect the engineers to come up with solutions which would yield more uniform outcomes than characterize either morphogenesis or brain function. Why would both develop solutions which involve multiple mechanisms, distributed function, and a regulative capacity, and which yield bounded variance as an outcome?

Under the circumstances, it pays to consider the possibility that perhaps there is actually greater similarity than is usually presumed in the nature of the tasks which the similar organizations have evolved to accomplish, and that the nature of those more similar tasks is such as to put a premium not on uniformity but on diversity. From this perspective, a noteworthy similarity between morphogenesis and brain function at the organismal level is that they are both information-gathering processes. This assertion requires some justification. Neurobiologists frequently think of the brain as a device for reacting to external information rather than for collecting it. Similarly, morphogeneticists tend to think of the creation of form as a process of unfolding, one for which external information is more or less irrelevant. Both notions have their origins in reasonable and productive simplifications appropriate for the early stages of exploration of brain function and morphogenesis, respectively. Reaction (the 'reflex') was initially the phenomenon of brain function most easily quantified and studied. For morphogenesis, the initial simplification was clearly described by E. B. Wilson in his classic *The Cell in Development and Heredity* (43): "The course of development is conditioned by both external and internal factors. The egg,

like the adult organism, is a reaction-system attuned or adapted to a particular set of external conditions. and it responds to changes in those conditions by corresponding changes in its mode of development.... For the purposes of our analysis, however, we shall treat the external factors as conditions of development rather than primary or determining causes. This is justified by the fact that the eggs of widely different animals give rise to its own typical product under identical external conditions;- the eggs of a sea-urchin, a snail, a worm and a fish undergo their characteristic transformations, each after its own kind. side by side in the same vessel of seawater. The specific differences of development shown by these various animals must be determined primarily by internal factors inherent in the egg-organization. It is these factors which we shall henceforward treat as the primary causes of development and as offering us its major problems."

Wilson's logic was impeccable, there must be internal differences which influence morphogenesis; equally clear was his recognition that a part of the problem of morphogenesis was being temporarily laid aside: the role of external factors. At the same time, there is good reason to now go beyond the initial simplifications: much of the puzzling complexity evident both in studies of brain function and in studies of brain morphogenesis becomes more manageable if one adds the same missing ingredient: a significant component of the organization underlying each is devoted to receiving information about the external environment (13). As Wilson clearly acknowledged, what is true of brain morphogenesis is true of morphogenesis more generally: no one doubts, for example, that the direction form which sunlight comes plays a significant role in determining the pattern of branches of a tree. Each part of a developing organism acquires information about other parts; many, in addition, gather information from the external environment. Similarly, each component of a brain gathers information from other parts, some of which are as well collecting information from the environment. Such information-gathering is a fundamental part of both morphogenesis and brain function, not an occasional add-on feature. It is important as well to distinguish such processes from 'reacting' with its accompanying implication that the system returns to status quo: both systems have the characteristic that changes in the external environment lead to more or less permanent (and more or less obvious) changes in internal state. It is this characteristic that warrants the term 'information-gathering'.

That both morphogenesis and brain function are information-gathering processes may help to account for some of the otherwise puzzling similarities in their characteristics. The environment from which organisms gather information displays some order but also a substantial amount of unpredictability. What this means is that the internal organization of any component involved in either morphogenesis or brain function which gathers information from the environment may change in unpre dictable ways. The redundant and distributed determination of higher order phenomena may well be the only way to design machines so that information-gathering and survival are compatible goals. Without such characteristics, the price of permitting unpredictable change in a component would be too high. Some degree of regulative behavior seems likely to be an inevitable consequence of redundant and distributed function, particularly if this, as seems to be the case, exists at several levels of organization and includes top-down regulatory processes.

The view of both morphogenesis and brain function as having significant information-gathering characteristics also offers some insight into the 'bounded variance' phenomenon which characterizes both. Some degree of variance from organism to organism and from time to time within an organism is of

course to be expected if environmental information, which is itself varying, is being collected. Some variance might also be expected simply due to uncontrolled noise in component or system function. What is intriguing, however, in the present context, is the likelihood that some of the observed variance is attributable neither to uncontrollable noise nor to information gathered from the environment but rather to a needed component of the information-gathering processes itself, the dice-throwing property discussed above. Both the evolutionary process and the immune system collect information about the environment by a process of registering its actions on internally generated variance. It would be surprising if this were not done by the nervous system and by morphogenetic processes as well.

This perspective not only provides an intriguing explanation for similarities between morphogenesis and brain function which are otherwise difficult to understand, but suggests some future lines of exploration which may be productive for understanding not only morphogenesis and brain function but biological organization generally. The perspective implies that important aspects of both morphogenesis and brain function (and probably evolution and the immune system as well) are determined not by anything idiosyncratic to these particular systems but rather by some more general set of rules and principles to which they are all subject (see Kauffman (23) for a related exploration). Given the present discussion, the likelihood is that these are rules and principles which govern information acquisition, transmission, and storage in what ever context it occurs. This notion is neither so spiritual nor so far-fetched as it might sound. Shannon established that information is a fully definable and quantifiable commodity, and Wiener's cybernetics has had a salutory impact on studies of both morphogenesis (41) and brain function (5). What has to my knowledge not, however, developed is a general theory of information in a form appropriate for biological systems (see Lloyd and Pagels (27) for what may prove a useful start in physics).

A biologically based information theory would require a way of quantifying information which reflects not only the improbability of a given state but also the degree of significance it has for the receiver: in biological systems the information conveyed by some polypeptide chains is clearly higher than that of others, even if they consist of the same number of amino acids. Similarly, a biologically useful information theory probably ought to include some factor related to the significance of the information content for the possessor; some organizations of molecules yield acceptable development or brain function, while other organizations of the same elements do not. Finally, such a theory would require a definition of information which is compatible with the idea of information addition in going between levels of organization, as discussed earlier in this essay, and perhaps a definition which is independent of a known catalogue of possible states, since it is uncertain whether such a catalogue is a priori enumerable for biological systems. A biologically based general theory of information, if it can be elaborated, might account not only for some of the similarities between different biological phenomena discussed in this article but additional ones as well. Evolutionary biologists have recently been forced to come to grips with a fossil record which raises the possibility that evolutionary change is not slow and continuous but rather involves periods of relative stasis interspersed with periods of rapid change (9). Morphogenesis too has something of this character, as does brain function. It is not inconceivable that such phenomena have an explanation in terms of permitted forms of information organization, and the mechanisms by which additional information can cause change from one form to another.

My primary concern in this article has been to call to the attention of neurobiologists and

morphogeneticists some similarities between the two fields the recognition of which may prove useful in both, and to suggest the possible existence of some more general biological principles worth exploring. In closing, though, it seems not inappropriate to note some of the possible relevances of this discussion for broader humane concerns. The conceptual frameworks of biology are not without impact on scientific practice and on human welfare generally. Sperry has written eloquently about the detrimental effects of 'microdeterminist' approaches in the sciences, and the desirable offshoots associated with an increased recognition of the levels of organization phenomena, including top down regulative processes (39). What I want to call attention to here is an additional feature specific to the understanding that variance is fundamental rather than either incidental or deterimental to successful biological organization. Science is, of course, an information-gathering process, and the importance to it of variance ought to be obvious. It seems worth entertaining the possibility that human societies more generally, like brains and the human species as whole, have a significant information-gathering function. and that variance among individuals is hence a characteristic which ought to be actively encouraged. In practice, we tend in our culture to measure individuals against a single standard, as if the objective of our educational and social organization were to create a particular, ideal sort of person. Machines certainly run more efficiently with standardized parts, but the effort to create them is a cause of considerable stress, both individual and social. Still more important, without variance the generation of novelty which is so important not only to poems but to sustained organization in the face of an unpredictably varying environment will be lost. It may be time to discard the metaphors of the machine age for not only the health of the biological sciences but that of our culture and species as well.

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