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The Next Big Problem in Developmental Biology[1,2]

JOHN TYLER BONNER
Department of Biology, Princeton University,
Princeton, New Jersey 08544

The "next big problem" I want to describe here is deceptively simple. We all recognize that in the fertilized egg there is a set of genes (along with some cytoplasm, a matter which we shall consider later) and that these genes give instructions that ultimately produce a complex adult. Genes are known to produce messenger RNAs which are then translated into specific proteins in the cell cytoplasm. How is it possible that this very limited process can construct, for instance, a complex animal with different parts and different cell types all of which exist in harmony, and not only produces a consistent form from generation to generation, but also permits that form to move, to function in an organized way, and on top of all that, to behave? The phenotype, both in its structure and in its activities, seems remarkably far removed from those first gene products, yet they are its origin. So not only do genes make proteins, but the proteins can in turn do things that, through a chain of events, lead to the ultimate result. This is the problem: how do those genes and their proteins control such distant, remote events.

One way to study the matter is to look more closely at the properties and the activities of the genes, especially of ones that seem to play a crucial role in development. This has been and is being very actively pursued in many laboratories with enormous success. It is the exciting frontier that is moving forward with dazzling speed. However, the steps that follow are equally important and exciting and they are the ones that have been more recalcitrant in revealing themselves, although we understand a large amount. But, as D'Arcy Thompson said, "Nature keeps some of her secrets longer than others."

I plan to discuss "the problem" here by examining how it arose in the first place: what is its evolutionary origin. This will bring me to the rather basic question of why we have development at all, and at the same time show that in an interesting way the rise of development is related to the rise of complexity. Within this setting I shall then try to organize some of the major concepts of development to show how they bear on the problem of how genes can have effects so remote from their immediate products. This will end with a brief discussion of behavior, the ultimate as a process that distances itself from the genome, and the ultimate in complexity.

THE EVOLUTION OF SIZE INCREASE

If one looks at the fossil record from the earliest beginnings and then follows it over billions of years, a striking fact emerges. The largest forms three and a half billion years ago were single cell bacteria, but with time the maximum size records steadily increased, first with larger cells and simple multicellularity, and then with the appearance of eukaryotic cells multicellular forms kept pushing the size limit upwards through geological time until finally we have the blue whales and giant sequoias of today. This progression does not mean that the smallest or middle-sized organisms have disappeared, for obviously they have not. It simply means that the upper size limits for many different groups of animals and plants has slowly increased over time.

When we ask why this might be so, it is possible to argue that there is often selection pressure for size change, or in some instances the change may be due to drift, especially in small populations. There are

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[1] From the Symposium on *Science as a Way of Knowing—Developmental Biology* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1986, at Nashville, Tennessee.

[2] This essay is an abstract of a portion of a forthcoming book, *The Evolution of Complexity,* in which detailed references are given.

many studies, both geological and ecological, which support the idea that size changes have occurred over time, but those changes may be either for an increase or a decrease in size. If size changes can result from selection, one escape from competition and predation is to become larger than any other organism. This is a reasonable explanation for the ever expanding upper size limits during the course of evolution.

COMPLEXITY AND SIZE

One of the automatic consequences of size increase is an increase in complexity. Complexity means the increase in parts and the interrelation of those parts. In living organisms the concept of complexity can be identified as differentiation, a form of division of labor.

If one is to argue that size increase is correlated with a division of labor within organisms one needs some way to gauge the accuracy of this generalization quantitatively. It is easy to measure size but difficult to measure complexity. One could say that since cells differentiate into cell types with different functions, then one might simply count the number of cell types in any animal or plant and this would be an index of complexity. The difficulty is that it is very hard to agree on how many cell types exist in large organisms such as trees, or ourselves. Nevertheless, the idea is useful even if one's estimates are considerably inaccurate. The reason for this is that one can make some general categories which have approximately a certain number of cell types, and then put all the appropriate groups of organisms in that basket. For instance, higher plants might be considered to have in the neighborhood of roughly 30 cell types, while vertebrates will have, by any system one uses for identification, over 120 cell types. This means that one can say with some confidence that vertebrates have more cell types than angiosperms, even though the exact numbers are to a considerable degree uncertain.

After examining the maximum and minimum size for different groups of organisms with numbers of cell types from 1 to over 120, it can be seen that there is clearly a trend despite the fact that for any one group the range of sizes might be enormous. Consider for instance that an angiosperm can be a minute duckweed or a huge eucalyptus tree, and a vertebrate will range from a minuscule fish to a giant whale. Yet despite the extremes of these minima and maxima for each group, there is clearly a trend: larger organisms are more complex. That this should be so can be explained on mechanical principles. A large organism simply could not function unless it had an appropriate division of labor which makes it possible to function. Size affects how an organism takes in food and oxygen, how it gets the essential substances to all its metabolizing cells, and how it eliminates its waste products. These and many other aspects of the running living machine are all size related; there could be no other way.

WHY DEVELOPMENT?

One invariant property of organisms is that the larger they are, the longer and more complicated their development. The reason for this is that virtually all organisms have a single cell stage in their life cycle. In some forms it may be a spore, but far more generally it is a fertilized egg. The reason that this is so has to do with the ubiquity of sexuality and the replication and recombination of the genetic material. In eukaryotes it occurs in chromosomes which are capable of mitosis and meiosis. This wonderfully clever system of duplicating and reshuffling the DNA for a new generation, a new life cycle, is so successful that once invented it has remained virtually unchanged (at least in any major way) during the evolution of all organisms from the first eukaryotes. Perhaps the most important point is that the uniting of two genomes by fertilization, the key element in sexuality, is possible only in single cells where two haploid gametes fuse to form a diploid zygote.

If, then, we have one stage of the life cycle that is large and multicellular (the adult) and another that, for reasons of properly controlling the genetic material, must be a single cell stage, the inevitable result is development. To put it in a very general way, development is the direct consequence of the evolutionary success of sex and size.

THE ACTIONS OF GENES

How genes behave and how they do things, as I said earlier, is an exceedingly active field at the moment, and here I want only to discuss a few small points that may give some insights into the power of developmental genetics.

First let me point out that genes can, by very small changes in their sequence of codes, make very radical changes in the structure of the proteins that they produce. This is because proteins have a tertiary structure which is contingent on certain amino acids on the protein chain reacting or associating with others, and depending where those key, mutually reactive amino acids are located, the folded, tertiary structure will be greatly affected. Suppose the protein is an enzyme and its activity depends upon its tertiary structure, then one small change in a nucleotide in the DNA will affect the ability of the enzyme to catalyze a reaction; it may decrease or eliminate that power or it may enhance it. But already the effect of the DNA is considerably removed from the end result. The enzyme may be allosteric, that is, can be affected by chemical combinations with other substances, including its substrate, which will either increase or decrease its reactivity (positive or negative cooperativity). In other words the tertiary structure has taken on a life of its own and can gain new properties by slight changes in its configuration due to the substances which surround it and combine with it. Those allosteric changes are not coded in the DNA; all that is coded is a chain of amino acids which produce a complex tertiary structure that is responsive to the chemical changes in its environment. This means that already at the level of proteins there are activities that arise which are not directly controlled by genes. The genes merely set the stage and provide the capacity to have those activities. In this simple example we already see how genes may produce remote effects beyond their immediate supervision.

To this simple picture, let us now add the fact that not all the proteins produced by genes are enzymes. Some genes produce regulatory proteins whose only role is to affect the action of other genes so that there is a network of cross reactions providing a hierarchy of gene functions. Such regulatory genes are known to play a major role in controlling key events during development; they are master switches.

Another level of complexity is seen in the phenomenon of pleiotropy. Here one gene may have numerous effects on the phenotype. A gene might affect eye color in *Drosophila,* but also produce changes in the gut. The effects of pleiotropic genes are often multiple. It is presumed in these cases that either the protein which is the direct gene product, or one of the substances derived from that protein through subsequent chemical steps, has quite specific effects in different parts of the body that do not seem in any obvious way related. Pleiotropy must be thought of as an indication of the hidden complexity of the action of genes and their subsequent effects through intertwining chemical pathways. This raises the vision of development as being a maze of interconnected chemical sequences of such dark complexity that one might wonder how we could ever unravel them.

SIGNAL-RESPONSE SYSTEMS

One way of stating the problem helps. Think of the developing organism as made up of a set of signals and a set of specific set of receptors for those signals. The genes are responsible either directly (if they are proteins) or indirectly (if they are small molecules) in producing both the signal substances and the receptors. In this way a communication system was set up within the embryo whereby events can be initiated or terminated or modulated. By making the receptor specific (and in some instances also the signal substance) it is possible to gain enormous powers of discrimination on where, in development, activation or inhibition will occur.

TIMING AND LOCALIZATION

One of the great problems in developmental biology is the timing of these signal-response systems so that they occur at the right moment, and furthermore that they are positioned in the right place. There are many interesting studies being made on the matter of timing mechanisms and hopefully soon we will have a better understanding of how they are controlled and how they relate to the genome.

The question of localization, or pattern formation as it is often called, is of enormous current interest. It is being attacked on two fronts. One is again by the developmental geneticist who is looking for the gene control of major patterns in the early embryos of nematodes, and especially *Drosophila.* There are genes which affect the major axes of polarity of the embryo and genes which affect segmentation. How those genes achieve these patterns is one of the genuinely exciting frontiers of developmental biology. But because so many aspects of localization, as was stressed earlier, are so far removed from the immediate actions of genes, this approach will not lead to the solution of all the problems of localization.

One of these approaches has been by mathematicians. The use of mathematical models in developmental biology is now a thriving industry that began some time ago. In recent years it has illuminated how it is possible, by means of reaction-diffusion models, or models involving mechanical parameters, to produce an enormous variety of pattern. This does not mean that the models can ever tell us what is actually going on inside the embryo—this can only be demonstrated by experimental dissection—but it can show us what is possible theoretically and, therefore, what sorts of things the experimentalist should look for. I think the importance of mathematics in developmental biology today and in the future is in danger of being underestimated. Those of us who work with molecules, with chemical reactions, with the cell biology of development are necessarily looking at the problem from a very narrow view. We are looking for solutions to simple questions; we have hardly any choice. But the mathematicians have already shown us that some of these little questions are in fact big ones, and we should pay attention to their models.

INTERTWINING CHEMICAL PATHWAYS

I would like to return to the idea that one chemical event in a cell leads to another, and these events may consist of long chains of chemical reactions that may branch and criss-cross in all sorts of intricate ways. Furthermore, they are affected by each other so that a product may inhibit (or stimulate) an early reaction in this way producing feedback loops (or there may be autocatalytic, feedforward loops). Presumably it is because of this kind of network that one has pleiotropic effects. One gene change might produce a variety of effects at the end of different but interconnected chains. Now let us consider such intertwining chemical pathways in different-sized animals and plants.

In small single cell organisms such as bacteria having all, or many chemical reactions connected does not raise too great a problem simply because the small size limits the number of steps and the number of connections. If a new mutation has diverse (pleiotropic) effects and one of them is deleterious, the result will be the death of the cell. But because bacteria can increase from a few cells and in a short time produce vast quantities of descendents, any lethal mutation will be cast aside, and any neutral or selectively advantageous mutation will increase at a rapid rate. These gene effects in bacteria are to some extent all-or-none and their rapid rate of turnover will multiply the good genes.

If we compare this situation with that of a large multicellular organism, we see that there must be some way to prevent excessive pleiotropy, excessive interconnections of all the gene initiated chemical pathways, for otherwise any chance of a successful mutation would be minute simply because even the smallest gene changes would have, if there were not some mechanism to prevent it, vast possibilities for destroying some essential process of the development or the function of the adult. Before discussing the buffering mechanism, let me give an example.

Breaking down cellulose into its component glucose molecules is a difficult task. This is not because cellulase is a difficult molecule for an evolving organism to invent, but because the cellulose is glued together in fibrils and a battery of enzymes is needed to separate the cellulose so that the cellulase can reach the cellulose. Only a very few invertebrates are known to have acquired the machinery needed to break down cellulose and no vertebrate, yet many animals, from termites to cows, eat cellulose. On the other hand, many unicellular microbes have independently invented the machinery: numerous bacteria, fungi, and protozoa. So the first conclusion is that it has been easier for the smallest organism to do this than large ones, for they have devised the magical enzymatic combination many times during the course of evolution, but among all animals it has been done only twice. The second conclusion is that for a large, complex animal it clearly must have been easier to take cellulose destroying microbes into its gut, and provide a favorable environment for these symbiotic slaves than going to the trouble (and making the extremely difficult evolutionary step) of making all the new enzymes itself.

Let us now return to the question of how large organisms with long and complicated developments manage to have genetic changes that run less risk of being lethal. To explain this I shall use a novel concept which I will call *gene nets.* The idea is straightforward. The activities of genes are grouped and these groups of genes and their immediate products and their subsequent chains of reactions are not all interconnected throughout the multicellular organism, but they are isolated into groups which are the gene nets. This means, for instance, that one might have a gene which produces a specific defect or change in one organ, such as white eyes in *Drosophila,* but because that gene is isolated in a gene net that is associated with the development of the eye, it has no other effects. (Presumably not all genes would be in gene nets, for those associated with, for instance, the basic metabolic machinery would apply to all the cells of the body. Gene changes relating to such basic metabolic process could indeed be pleiotropic, such as the eye color-gut defect mentioned earlier. But successful metabolic mutations are rare because they are not protected and are vulnerable. This is one area of the genome where one sees little change during the course of evolution of major groups of organisms.)

It is by the formation of gene nets in complex organisms that heterochrony is possible. In a classic example, in salamanders in general the larval stage is aquatic and the larva has gills, while the adult has lungs. In the Mexican *Axolotl* the gonads ripen in the larvae which may never reach adulthood, always remaining aquatic. Here we have two gene nets: one for the production of lungs and one for the ripening of the gonads. The timing of these two gene nets can be shifted so that the order in which they appear can be reversed. This is heterochrony, and such a shift would not be possible if both structures were interconnected on the same set of chemical reaction pathways. So gene nets make it possible not only for genetic mutation to affect different parts of a large organism without the danger of having adverse effects on other parts, but also to shift the timing of developmental events, often producing major evolutionary steps.

EXTREME DISTANCING OF THE FINAL DEVELOPMENTAL RESULT FROM THE INITIAL GENE ACTION

Thus far the principles of how the phenotype may be far removed from the initial gene product have been examined. Next I want to discuss two examples in which that distance seems remarkably remote. The first is the particularly interesting case of the social insects, and the second is behavior.

Social insects

In the case of social ants, bees, wasps, and termites there is not just a division of labor within any one individual, but between individuals as well. Besides the male and the queen there is a large family of neuter workers which, in one of the more complex social insects, may have a number of different sizes and size-related shapes. Furthermore, their activities within the colony represent a clear division of labor. The smallest workers help the queen and take care of the larvae in the nest. The middle-sized workers usually specialize in food gathering and storing. The largest workers are the soldiers that are specialized for guard duty and keep out unwanted predators.

Not only does this division of labor exist, but like the division within an individual organism, the parts (individuals) are genetically closely related, and clearly the difference arises from external influences. For instance, in the case of termites the soldiers are known to give off an inhibitor that prevents the young nymphs from molting into soldiers. If all the soldiers are removed from a colony, the inhibitor they give off disappears and immediately new soldiers appear at the next molt. By means of such inhibitors a balance between the castes is achieved and we have what might be considered pattern formation (*i.e.*, controlled proportions) at the level of the colony. This is, in essence, a developmental stimulus-response mechanism between individuals rather than within individuals. The inhibitors between individuals affect the endocrine balance within the nymphs and in this way the direction of their differentiation is guided. If we now turn this picture around and ask how the genes control the proportions of the castes, one can see that there is a considerable hierarchy of events. The signal-response systems act not only at the level of the cells, but at the level of the organs within the individual insects, and then ultimately at the level of the colony, that is, between insects. There is a long path from the first proteins made by the genes to the integration of a colony of social insects.

Developmental plasticity and the formation of the brain

It is evident from the example of social insects that the development of the workers is to some degree plastic and the direction in which they are pushed depends upon external factors such as inhibitor substances and other external factors which I did not discuss such as nutrition. There are many examples where a particular developmental pathway may be influenced by the environment. For instance, the crowfoot, an aquatic buttercup, will develop entirely different-shaped leaves depending upon whether they are under water or in the air.

Another kind of plastic development may be seen in the construction of the vertebrate brain and nervous system which is of particular interest. It has been well established that the exact number of neurons needed in the brain is not fixed. Instead a considerable excess of neurons is made and only after they have moved about in the early forming brain and found connections does the number become fixed. All those that did not make it into the organized, connected network of nervous tissue die. This means that potentially there could be considerable variation in the number of neurons in two brains of closely related animals. We do not understand what are the control mechanisms for connecting of the young nerve cells. One could imagine that a combination of chance movement and early function might play an important role, but still this must be thought of in a background of genetic information. It will be very important to understand this process in greater detail.

Behavior

As I said earlier, development is the ultimate complex process that is far removed from the first gene transcriptions and translations. Furthermore, it is the ultimate in complexity, and the ultimate in plasticity. We need only think of our own thoughts to be convinced that is the case. It is so evident that we may even question that genes have anything to do with our behavior, but only provide the neuronal setting from which behavior can emerge. It is much easier to obtain some picture of the situation if we briefly examine the behavior of some non-human animals.

Consider the case of predator avoidance in birds. As we know from some of the early experiments of the pioneers in ethology, if a hawk-like silhouette is pulled on a wire over young goslings they will scuttle for cover, even though they may be only a few hours old and have never seen a hawk before. The shape is quite specific, for reversing the direction of the silhouette (which makes it look like a goose) does not cause the alarm reaction. From this we must conclude that this is a complicated reaction which involves recognizing a particular visual pattern and hooking it up with a specific response pattern. Since it is ready to operate at birth we assume that it has a genetic basis.

It is not at all clear how the genes specify such an involved bit of behavior. One can only assume that the process is very complex, involving many chemical steps, building up a signal-response system which involves widely different and separated parts of the body. This clearly has occurred during development, and therefore it is a particularly fascinating problem in developmental biology, one we hope will receive careful attention in the years to come.

Let us now expand on this theme with examples of ever increasing complexity and plasticity. Another form of predator avoidance in birds is seen in mobbing. A flock of crows will, for instance, surround a large owl and make a tremendous commotion cawing and lunging at the owl. It is an assumed that this behavior helps to draw attention to the source of danger so that no crow is caught unawares, and it also is often successful in making the predator move off to another territory. There is considerable evidence that at least some of this behavior is learned. In a set of elegant experiments, E. Curio and his colleagues (1978) set up two cages so that one European blackbird saw an owl and the other a harmless Australian honeyeater. The first bird began to energetically mob the owl, and the other bird witnessed all of this frenzy. Before long it began to mob the honeyeater (which it never had done in a control experiment). The bird that had been taught the presumed dangers of the honeyeater was, in the next experiment, presented with that same harmless bird which it proceeded to mob, and a new, naive bird, which could also see the honeyeater, soon followed suit and mobbed it too. This bit of cultural information was passed on in five other passages from a new learner to a new naive bird. In this case we assume that the advantage of such learning to a bird is that if new predators enter the territory it will not take thousands of generations to learn the new danger; it can be passed on in a matter of minutes. The flexibility which learning imparts to behavior could conceivably be of enormous adaptive advantage to an organism to cope with rapid changes in its environment.

One final example where there is even greater flexibility in behavioral signal-response system may be seen in African vervet monkeys which have been extensively studied by R. M. Seyfarth and D. L. Cheney (1984). They show that these monkeys have three vocal signals, each one for a different danger. One, which is the signal for an eagle, causes all the members of the social group to scurry for protection in clumps of bushes. Another distinct alarm call means leopard, and to this they rush out into the most open spot where they are least likely to be ambushed. Finally, the third call is for snakes, also a dangerous predator (in this case usually a boa constrictor). Upon hearing this signal the monkeys quickly look around the ground, and then scamper up the nearest tree. It is clear that to one situation, predator avoidance, the vervet monkeys have produced a variety of signals to accommodate their multiple needs. We do not know how much is inherited and how much is learned, although there must be a large component of the latter. The main role of the genes is to set down an anatomical structure, the nervous system including the brain, which is capable of such a variety of flexible responses.

CONCLUSION

All behaviors, including the ones described above, are the product of genes. Even their amazing plasticity is possible only because of the genes and the proteins they make. What the genes have produced over the course of evolution of larger and more complex organisms seems to have become increasingly remote from those initial gene products. The remoteness lies entirely in the number and complexity of the intervening steps. Let me briefly review the generalizations I have made about those steps.

Following the first proteins that are translated, new properties may emerge, even in the proteins themselves, that can be explained by the sequence of the amino acids. Those properties include changes in tertiary structure which lead to the flexibility of allostery. These proteins as enzymes, or substrates, ultimately control a whole series of interlocking, sequential chemical reactions that produces the obvious morphological changes we see during development. Those changes become self regulatory by means of feedback and feedforward loops, and they often produce ultimately a complex of signal-response systems which also are key regulatory elements during development. The signals and responses can occur at different levels, cells, multicellular individuals, and even in social groups. Moreover, the signals can go from one level to another, in this way binding the levels by a system of intercommunication. With increase in size these communication systems have become grouped into what I have called gene nets, and each gene net has achieved some degree of autonomy so that it can accommodate internal changes without necessarily affecting the workings of other gene nets in the developing organism. Such postulated partitioning is a way to handle increased complexity.

The zenith of developmental complexity is the evolution of the nervous system and the brain. It gives rise to behavior which appears to be a very different kind of complexity from anatomical intricacies. Furthermore, its cellular development and the development of its activity, especially in the interplay of rigid, determined activity with highly flexible activity, seen especially in learning, seem to be two totally separate mechanisms that complement each other. Behavior is a new kind of development, for indeed it is a new kind of invention of the genome, and for that reason alone it is intimately part of development.

In the great span from bacteria to the monster plants and animals of today, there has been an increasingly elaborate matrix of steps between the genes and the end result. That is the great problem of developmental biology.

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