



In Context

Number 23 Spring 2010

The Newsletter of The Nature Institute

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Dear Readers,

In this issue, as in so many of our past issues, you will find content representing two poles of science: on the one hand, we engage mainstream analytic science, with its quantitative and reductionist tendencies (see the feature article on epigenetics), and on the other hand we present brief qualitative and descriptive articles about plants and insects (Notes and Reviews section). Bringing these aspects of science together, overcoming any one-sidedness, and making a whole out of them is very much what The Nature Institute is about.

Doing this well and making a difference in the world requires a certain wholeness in the Institute itself. The research, of course, occupies a central place — Craig's whole-organism studies, Steve's current work in epigenetics, and Henrike's interrelated researches involving light, astronomy, and projective geometry. And all of us are concerned in one way or another with the philosophy and epistemology underlying a qualitative science.

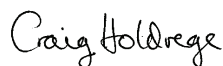
Such research requires a good deal of individual effort, as well as mutually stimulative conversation. But when we turn toward the educational side of the work, it's much more a group activity, where the qualities of interaction become central. Lectures, workshops and courses — both at the Institute and elsewhere — involve us in a larger community, and the building up of this community is fundamentally important to the success of the Institute.

Then there is the widest circle of communication, involving our various publications — newsletters, articles, and books. On the book front, we are happy to report that the University Press of Kentucky has recently reissued *Beyond Biotechnology: The Barren Promise of Genetic Engineering* as a paperback. You'll find ordering information at <http://natureinstitute.org/store>.

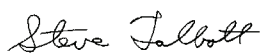
We try to keep you informed of our entire range of activities through the newsletter you are now reading. You may not be aware, however, that we have a second newsletter called *NetFuture* — electronic only — which is the main venue for the bulk of Steve's work. It has lately been focusing heavily on the revolutionary developments in genetics, epigenetics, and molecular biology in general. You can check it out (and take out an email subscription if you wish) at <http://netfuture.org>.

All in all it makes for a very busy time for a small organization! We are currently consulting with a circle of friends and supporters in order to assess the past twelve years of our existence and to look as openly and creatively as we can toward the future. Given the state of the economy, it's a difficult time for many nonprofits, and we have not been spared the additional challenges — all of which makes it a good time to consider where we have been and where we would like to go. We will be happy to receive any thoughts you may have about our work and future directions.

Craig Holdrege



Steve Talbott



The Nature Institute

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The Drama of Milkweed Pollination

Craig Holdrege

In the Spring, 2009 issue of In Context we introduced you to the milkweed plant and its life cycle. Here we add to that picture, with a special focus on the remarkable sequence of events resulting in the pollination of the milkweed flower.

When you see an old field, the robust common milkweed plants stand out among the much sleeker grasses, asters, or goldenrods. Common milkweed has thick stems and expansive leaves that, in shape and size, look more like the leaves of a plant growing in shady woods than in a sunny old field. In the warm summer days of late June and through much of July, the large spherical heads of flowers unfold on the upper part of the stems. The individual flowers are actually quite large for a field plant and they produce large amounts of concentrated nectar. Their scent spreads out into the surroundings. When in flower, a colony of milkweeds attracts—day and night—a great variety and number of insects of all different shapes and sizes. For several weeks in summer milkweed becomes a microhabitat with a singular concentration of insect life.

After the flowers wilt, the fruit pods begin to expand. While relatively few fruits form out of the multitude of flowers, those that develop grow large—much larger than those of other old field community plants. The pods swell and orient themselves upward, a contrasting gesture to the globes of flowers. Each pod is full of seeds, seeds that are large and heavy. But they have the light feather-like extensions of the



Figure 1. A common milkweed plant beginning to flower.

white comas that allow them to be carried away on a breeze when the pods split open. It is almost as if the upward pointing pods are prefiguring what is to come—the upward lift of the coma-bearing seeds that disperse into the larger environment. As with all stages of milkweed, both pods and seeds provide nourishment to insects.

One salient feature that informs milkweed is its exuberant and robust growth. Underground it spreads year to year, forming a network of thick rhizomes out of which the above-ground shoots grow. The thick shoots bring forth large, spreading leaves. All these parts of the plant contain the milky sap, which is continually produced as the plant grows and develops. A marked transformation in substance and form occurs as the many large umbels (flower clusters with all the flower stalks originating at the

apex of their common stem) unfold in the summer light and warmth. As the stems and leaves are rich in milk sap, so are the flowers rich in sweet nectar.

Flower Morphology and Pollination

While the form of the leaves in common milkweed—and other members of the genus as well—is simple and the shape hardly transforms from bottom to top of the stem, the flowers are highly complex and differentiated. It took a good deal of detailed botanical study to identify and relate milkweed flower structure to the anatomy of other flowers.

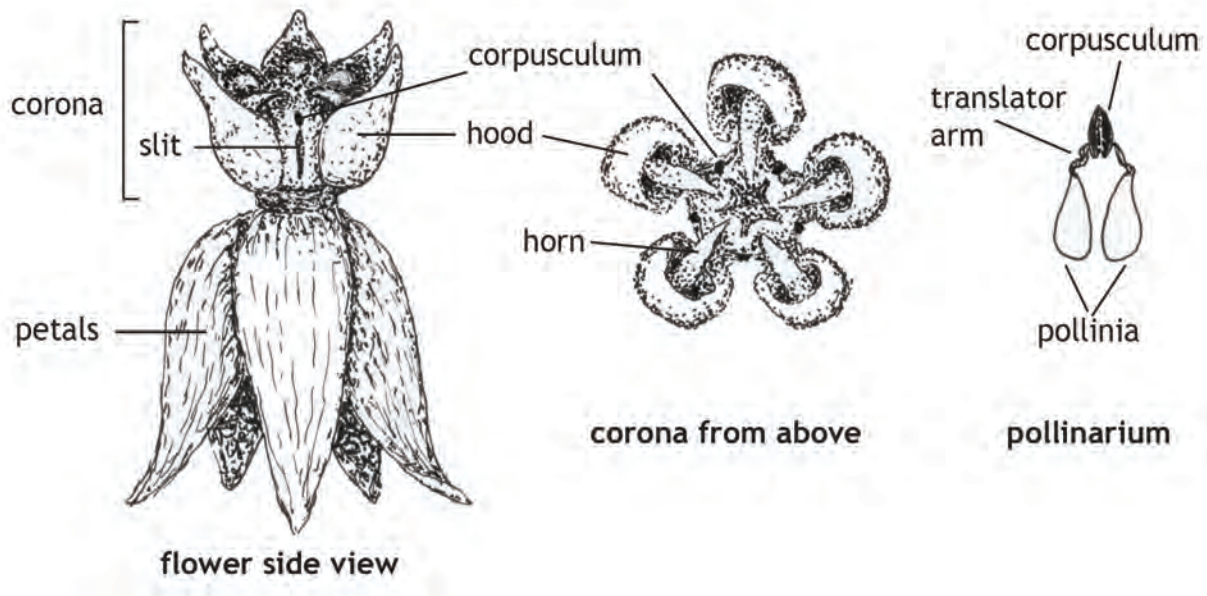


Figure 2. Flower structure of common milkweed (*Asclepias syriaca*). See text for description.
 (Photos and illustration: Craig Holdrege)

When the flower opens, five small green sepals fold back and then five larger elliptical white to pink petals also fold back and come to lie more or less parallel with the flower stalk. In most “typical” flowers of other kinds of plants you find the circle of petals surrounding a circle of stamens, whose anthers release pollen, and then in the center of the flower the pistil in which the seeds will develop. Neither the pistil nor the stamens are clearly recognizable in the milkweed flower. Rather, a number of accessory organs form out of the partially fused stamens and pistil. Figure 2 gives a diagrammatic representation of the milkweed flower. Above the petals is a so-called corona consisting of five cuplike

hoods out of which extend little curved horns. The hoods hold the nectar that attracts so many insects on warm, sunny summer days. In between the hoods are little vertical slits. Each slit opens into a stigmatic chamber. (What it has to do with the stigma, we will see further below.) Above the slit there is a tiny black knob, the corpusculum. What one doesn’t see is that the corpusculum has two little arms (called translator arms) that extend into the two upper sides of the chamber. Each arm attaches to a golden package of pollen, called a pollinium. Each of the pollinia houses hundreds of pollen grains. Unlike the pollen in most flowers, which is released from the anthers while they are still

attached to the flower, in milkweeds the pollen remains contained within the pollinia until it comes in contact with the stigma of a flower. Only orchids—also plants with complex flowers—package their pollen in a similar way.

The only way for the pollinia to escape their chambers is via insects. As already mentioned, milkweed flowers are visited by a multitude of insects in search of nectar—which they find in generous supply. Not only is the nectar very rich in sugar content, being up to 3% sucrose, but the supply is also renewed over the life of the individual flower. Milkweed flowers produce much more nectar than the many insects feeding on it could ever remove.

While the insects are moving around on a flower—they sometimes go from hood to hood on a single flower—one of their legs may slip into a slit. I have often observed honey bees and flies struggling to pull a leg out of the slit. Most often it succeeds by pulling its leg upward whereby the leg hooks into a groove on the corpusculum at the top of the slit, and as a result the insect pulls the whole pollinarium—corpusculum, two translator arms and two pollinia—out of the stigmatic chamber. One study showed

that a bumble bee picks up on average a new pollinium every 2 to 5 hours and that the same pollinium remained attached to the legs for on average 2.5 hours, while if attached to the mouthparts, the pollinium stayed attached for 10 hours. As an insect continues its nectar foraging, it often accumulates multiple pollinaria. One pair of researchers reported finding up to 35 pollinaria on a single insect; sometimes they are hooked together in chains of ten or more dangling from an insect's leg. Most often one sees honey bees (*Apis mellifera*) with many pollinaria attached to them (Figure 3).

Smaller insects—I have observed mainly flies—may be unsuccessful in removing a leg from a slit and the limb will tear off in the process. I have also seen dead flies hanging from a flower with a leg still caught in a slit. Larger pollinators like bumble bees and honey bees are more likely to extract pollinaria without losing a body part.

What happens to the pollinaria? Many will simply drop away or be rubbed off as the insect moves around. A few will find their destination in another flower. And just as the removal of the pollinaria is both a haphazard and narrowly

A



B

Figure 3. A: A honeybee moves through an umbel of milkweed flowers. B: Close-up of a honeybee on a milkweed flower with multiple pollinia dangling from its legs—although difficult to see in a black-and-white image. (Note the slit and corpusculum [dark spot] between two of the hoods of the flower in the lower left of photo B.) (Photos: Craig Holdrege)

constrained process, so also is pollination. First, something remarkable and absolutely essential for pollination occurs with the pollinarium itself. After an insect has been carrying around a pollinarium for about ninety seconds, the pollinarium dries out and in the process the translator arms rotate ninety degrees. This torsion is highly significant because it brings the pollinium into a position that allows it to slip into a slit when an insect moves over one. Before the torsion, the broad side of the pollinium usually faces the slit as the insect crawls along; afterwards the narrow side of the pollinium is in line with the slit so that if the insect is moving at just the right height over a slit, the pollinium can slide into the stigmatic chamber. As the insect moves ahead, the translator arm breaks and the pollinium remains behind. Once in the chamber, one edge of the pollinium rests against the receptive wall of the stigmatic chamber. While in most flowering plants the stigma is open to direct contact with the air and visiting insects, the five receptive stigma surfaces in milkweeds are enclosed within five stigmatic chambers, open to the world only through the narrow slit. So in milkweed flowers both pollen grains and stigmatic surfaces are housed in enclosed structures.

Only when the pollinium slides into the stigmatic chamber can this encapsulation be overcome. Everything I will now describe is visible only when one dissects flowers at different stages of the pollination process and looks at the structures under a microscope. The stigmatic chamber is the source of nectar for the hoods, and when the pollinium is inserted into the chamber it is bathed in nectar and begins to swell. Within a few hours the edge that is in contact with the receptive inner surface of the stigmatic chamber breaks open and multiple pollen tubes grow out of the pollen grains. The tubes grow down the style and into one of the two ovaries of a flower. An ovary contains a couple of hundred ovules and each one needs to be fertilized by the nucleus from one pollen tube. Interestingly, when fertilization occurs, virtually all the ovules are fertilized—one rarely finds milkweed pods with just a few seeds.

One could at first think that the highly specialized pollination apparatus, which provides a seemingly perfect fit between pollinium and stigma, would guarantee successful fruit set. But this is not the case. In the first place, the specialization also means that relatively few pollinia actually are successfully inserted into a stigmatic chamber. Secondly, researchers discovered that common milkweed is self-incompatible. This means that the pollinium from a flower that is inserted into a flower of the same colony will normally not bear fruit. The pollen tubes grow into the ovary but the seeds do not develop. Because insects are moving largely within a given colony, it is likely that most

of the pollinia inserted come from flowers of the same colony and will therefore not lead to successful fruit set. One study using radioactively labeled pollinia found that a third of the pollinia inserted were from the same umbel and most of the other inserted pollinia came from the same colony; only a few were carried to other colonies and successfully inserted.

As if this “inefficiency”—we could also call it over-abundance—were not odd enough, even when researchers cross-pollinated flowers of related *Asclepias* species by hand, fruit set never exceeded 20% and was usually considerably lower. Thus, overall, the specialization of milkweed pollination, at least in relation to successful fruit formation, is connected with a low vitality. If one looks, however, at a milkweed colony from the perspective of the many insects that feed on the flowers’ nectar, milkweed is contributing significantly to the vitality of those animals. Of course, the picture is more complex if we think of the occasional death of mainly smaller insects unable to remove a limb that has been caught in a slit.

One interesting feature of the relation between flower structure and insects is that although all milkweeds have such specialized flowers, they are visited by and can be pollinated by a wide array of insects. The nectar also attracts ants and small beetles that usually contribute little toward pollination, but reap the benefits of the ample nectar supply.

Milkweed’s highly specialized flowers and the intricate pollination process bring into focus how an organism extends beyond itself through its relations to insects in its environment. And as we will see in a subsequent essay, the story of the relation between common milkweed and insects is even more complex: a number of insect species and common milkweed have co-evolved, resulting in the insects becoming so specialized that their lives are inextricably intertwined with the plant.

REFERENCES

For the references, which have been omitted from this article, please contact the author (craig@natureinstitute.org).

Insects: Extending into the Environment

A remarkable book has recently been published by Adonis Press—an English translation of a German work by the biologist and ecologist, Andreas Suchantke. The book is Metamorphosis: Evolution in Action and presents some of the fruits of Suchantke’s decades of research. Here we extract a small section from a chapter on insects. The text has been abridged and adapted for its appearance here. All the drawings are by Andreas Suchantke. (See the list of the book’s chapters in a separate box.)

The insects (and the other arthropods, crabs and spiders) have an external or exoskeleton, which extends over the whole body, including the legs. The musculature is internal and enclosed in the legs by the tube-like exoskeleton, which requires completely different kinds of joints from those found in animals with a radial endoskeleton (Figure 1). Being encased in an exoskeleton means being sealed off from the environment, coated in a totally dead substance, chitin. After each moulting this chitinous armor is secreted in liquid form through pores in the epidermis and hardens immediately into a wonderfully sturdy, shiny layer. In order to grow, the insect must occasionally free itself from this covering, which, being dead, is incapable of growth.

This shielding tendency is countered by organs that make intimate contact with the environment, such as the sense organs, the extremities, the wings. Depending on which of these two tendencies is dominant, the insect will be more open towards its surroundings or more closed off.

[Let us] take a closer look at the bodily organization typical of insects. The first feature that stands out—not in all, but in very many cases—is the division of the body into the three sections of the head, the thorax and the abdomen (Figure 2). On this subject Goethe remarked:

All reasonably developed creatures show three main sections in their external structure. How perfect in this regard, for instance, are the insects! Their body consists of three parts, which perform different life functions and through their reciprocal effects and interconnections raise organic existence to a higher level. The three are the head, the middle and the rear part. If the said parts are very distinct and joined only by means of thread-like tubes, this indicates a state of perfection. This is why the key event in the successive metamorphosis from caterpillar into insect is the successive separation of the functional systems, which in the caterpillar still lay cocooned in a partially inactive and unexpressed condition.

In its overall organization the “perfect” insect retains much of its original segmentation, even though nothing of these identical segments (often still clearly discernible at the larval stage) is externally visible. This is very much in keeping with the fact that limb primordia [the embryonic buds out of which limbs later develop] form on all body segments during embryonic development. In some insects they persist on most segments into the larval stage (butterflies, sawflies), while in others, such as house

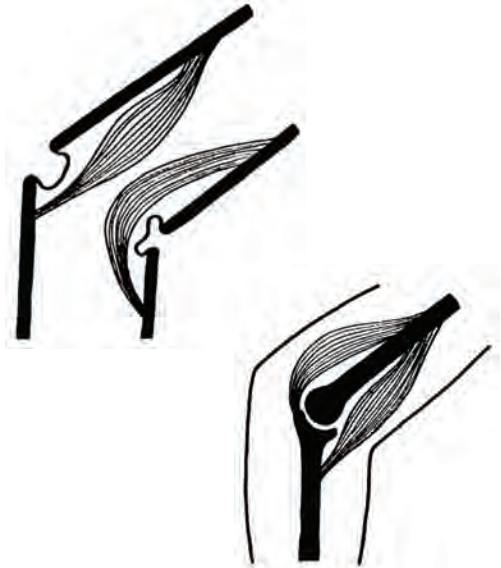


Figure 1. Relationship between skeleton (shown with heavy black lines) and musculature: polarity between vertebrates (below) and arthropods (insects and crustaceans, above) in the musculo-skeletal organization.



Figure 2. Bee: a female forager with a cargo of pollen on her rear legs. The three different body regions can be clearly distinguished, but in the hymenoptera (bees, wasps and ants) these do not quite correspond to head, thorax and abdomen: the first abdominal segment is merged into the thorax (their point of conjunction is discernible as a faint line).

fly maggots, they disappear. On mature insects (imagos) [in addition to the normally present legs and wings] limbs can appear in other forms. In dragonflies they take the form of prehensile organs that play a role in mating, in earwigs they become pincers (used, among other things, for pulling their wings out of the pouches into which they are intricately and tightly folded—see Figure 3).

More significant, however, is the occurrence of limb primordia on the head, which also consists of several merged segments. Here they are recognizable by the fact that they are arranged in pairs and move by means of joints as feelers and as “chewing limbs” (in insects the upper and lower jaws move horizontally). The feelers are particularly interesting. In many cases they will be found to have kept their original limb-nature. This is especially clear in ants, which use them to exchange tactile vibrations, and even to milk aphids, i.e., by stimulating them to excrete a sugar-rich substance (Figure 4).

Limbs become sense organs, or combine the related functions of perception and movement in one structure. Crickets hear with the tympanic organs located on their long hindlegs; moths, as recent studies have shown, hear with their wings; houseflies taste with the soles of their feet, etc. Completely different from the vertebrates (and many groups of invertebrates) is also the remarkable, highly differentiated structure of the eyes. They do not take the form of spheres set into the head, as in vertebrates and humans (aptly dubbed “gulfs of the external world” by Rudolf Steiner), but consist of bundles of long tubes radiating out into the whole periphery (Fig. 5). The eyes of a large dragonfly, which consist of large numbers of these so-called ommatidia—up to 28,000 in each eye—surround the whole head, enabling all-round vision. This vision is accompanied by constant head movements and at any moment can propel the insect into instant flight when it sights prey, a rival or a female: perception and movement are one.

Through the multifaceted subdivision of the field of vision as a result of the integrated rows of individual eyes, the tiniest movements can be registered. Added to this is an ability to magnify time. This is familiar to anyone who has tried to catch flies by hand. To have any hope of success one must approach the fly so slowly that it does not notice the movement, and then pounce suddenly; but even then one is usually much too slow. To describe such a reaction by saying that seeing stimulates movement is to formulate things too dualistically. Here seeing *is* movement. It can be so compulsive that an insect, once it has set its course for a light source, will hold it unflinchingly and be literally “sucked” into it (Figure 6).

Bees are different in this respect, in that they can fly from a newly found food source straight back to the hive, even though their outward flight took a different route. It would seem that insects do not live “in themselves,” but extended into their surroundings. This means that they are in reality much larger than the tiny physical speck of a creature that our eyes take in. The dragonfly is one with the realm of air and light in which it lives, the bee with its realm of scent and color, the butterfly with the play of light and shade in the world of color it inhabits. This is borne out by the peripheral quality of their sense organs, by their wraparound eyes, and their feelers, which are limbs that have become sense organs.
Insects are sensory-limb beings.

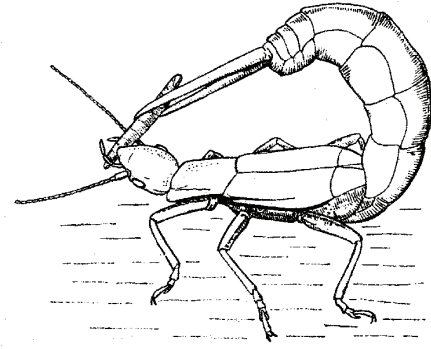


Figure 3. An earwig (*Forficula*) brings food to its mouth by means of its abdominal pincers. (After Dettner and Peters.)



Figure 4. An ant rubs an aphid with its feelers, stimulating it to produce a droplet of sugar from its anus. (From Dumpert.)

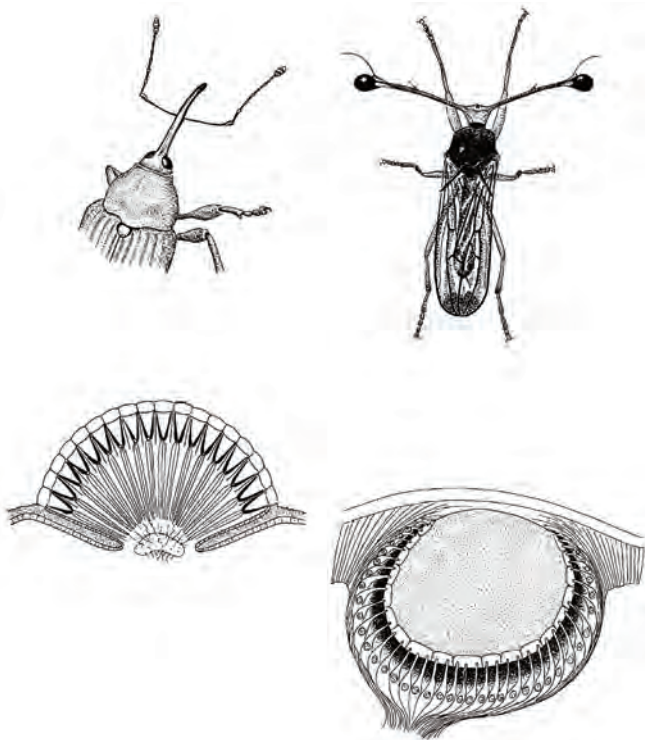


Figure 5. "Sensory limbs." Above left: jointed feelers on a weevil (*Balanus nucum*). Above right: an African fly (*Diopsis*) with its eyes grotesquely perched on the ends of long stalk-like head appendages. Below: polarity of eye structure in the compound eye (schematic) of insects, raying out from the head (left); and the "hollow," ball-shaped eye, embedded in the head of a marine polychaete worm (right). (After Kaestner.)

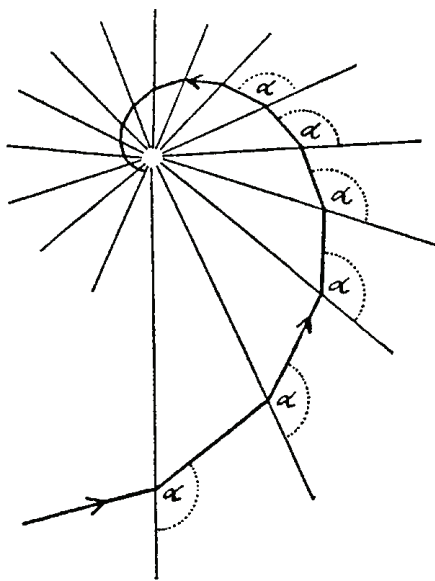


Figure 6. Constant angle maintained by a caterpillar crawling towards a light source—and finally being "burnt" by it.

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Metamorphosis: Evolution in Action

BY ANDREAS SUCHANTKE
Translated by Norman Skillen

Available from Adonis Press,
321 Rodman Road, Hillsdale, New York 12529.
<http://www.adonispress.org>.

The book is hardcover, large format,
324+11 pages, \$50.00.

Goethe at MIT

From MIT Press — that bastion of technical and engineering expertise — there now comes a surprising and remarkable production. On the highest quality paper, with a hardcover binding worthy of the diaries of Picasso, with a graceful, informative introduction and appendix by Gordon L. Miller, and above all with numerous spectacularly beautiful photographs, also by Miller, MIT has presented us with a true gift: a luxuriously blooming edition of Goethe's 1790 work, *The Metamorphosis of Plants*. The book is a wonderful validation of the scientific worth of Goethe's pioneering researches on morphology — researches that, according to historian Robert J. Richards (quoted in the introduction), “seeded a revolution in thought that would transform biological science during the nineteenth century.”

Just as we can recognize a certain unity among the diverse forms of apple tree, so, too, we recognize a much broader unity embracing the entire plant kingdom and distinguishing it from animals. Goethe, by studying intensely many different plants in a variety of contexts, came to an inner realization of that unity, which he called the archetypal plant, or *Urpflanze*. He understood that this could not be any physical plant. But at the same time, if we recognize a unity among plants, this unity must in one way or another be characterizable, and the characterization would point to essential features of the ideal plant. Goethe attempted to sketch some of these features in his *Metamorphosis of Plants*. In Miller's words, Goethe “coupled rigorous empiricism with precise imagination to see particular natural phenomena as concrete symbols of the universal principles, organizing ideas, or inner laws of nature.” In the plant, these laws manifest as patterns of metamorphosis.

References to “ideal plant” and “inner laws” might seem foreign to the spirit of modern biology. However, even at the level of molecular biology the scientist is continually referring to “regulation,” “coordination,” “information,” and “communication”— all pointing to an inner coherence and to guiding principles that shape the organism as a developing form.

Goethe tried to be as fully conscious as possible of his own cognitive processes. He concerned himself a great deal with the potentials and pitfalls of scientific practice. In the book's appendix, Miller sketches Goethe's own sense of method, which the German artist and scientist once described this way:

If I look at the created object, inquire into its creation, and follow this process back as far as I can, I will find a

series of steps. Since these are not actually seen together before me, I must visualize them in my memory so that they form a certain ideal whole.

At first I will tend to think in terms of steps, but nature leaves no gaps, and thus, in the end, I will have to see this progression of uninterrupted activity as a whole. I can do so by dissolving the particular without destroying the impression itself.

(For a brief discussion of how this works in practice, see “Can We Learn to Think Like a Plant?” at <http://natureinstitute.org/txt/st/mqual>. The article draws heavily on the late Ronald Brady's consideration of leaf sequences.)

In carrying out this work, one necessarily rises (applying Goethe's terminology) from understanding to reason. That is how one penetrates to the heart of nature:

The intellect will not reach her; man must be capable of elevating himself to the highest reason to touch the divine, which manifests itself in the archetypal phenomena (*Urphänomene*) — both physical and moral — and dwells behind them and is their origin.

The divine works in the living, not in the dead; in what becomes and transforms, not in what has become and is fixed. Therefore reason, with its tendency toward the divine, has only to do with becoming and the living; but the intellect with what has become and is already fixed, so that it may make use of it. (Translation modified by C. Holdrege.)

In an age of technologically dominated science, there is a good case to be made that Goethe's practice and his methodological reflections have become more, not less, relevant to the scientific enterprise. This book nicely supports that case. ST

Here's the book information:

JOHANN WOLFGANG VON GOETHE
The Metamorphosis of Plants
with an introduction and photography
by Gordon L. Miller

Cambridge MA: MIT Press
Hardcover, 123+31 pp., \$21.95.

More Unintended Effects of Genetic Manipulation

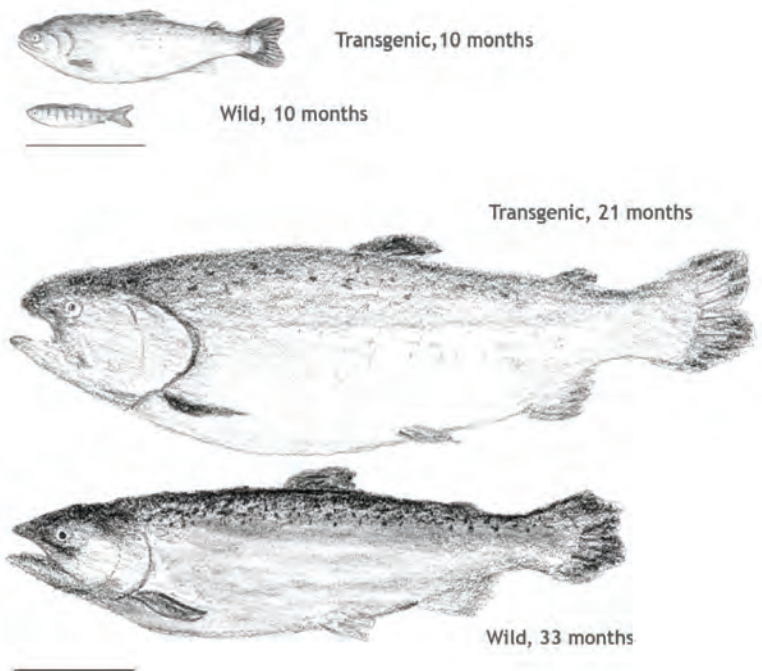
The Nature Institute's project on the "Unintended Effects of Genetic Manipulation" has continued to grow. In addition to adding many reports on the results of genetic manipulations of plants to our nontarget.org website, we've now posted our first group of reports on experiments with transgenic animals. The findings could hardly be more dramatic, as the following report titles may suggest:

- Tilapia fish engineered for transgenic expression of growth hormone had deformed heads and backs, atrophied gonads, and lower mineral content.
- Transgenic expression of sheep growth hormone in sheep increased the incidence of reproductive problems and premature death.
- Sheep engineered to produce transgenic proteins in their milk had unusually high morbidity and expressed a milk-specific protein in their spleen, liver, and other organs.
- Transgenic expression of a mouse milk protein impaired mammary development and function in pigs.
- Transgenic pigs with elevated levels of growth hormone were infertile, pre-diabetic, and experienced joint problems.
- Sheep growth hormone expression was highly variable in transgenic pigs, whose bodies had more protein and water and less fat.
- Transgenic pigs expressing bovine growth hormone had lower appetites, enlarged organs, gastric ulcers, and other health problems.
- Transgenic goats engineered to secrete the human protein cholinesterase into their milk produced less milk, with lower fat and lactose levels and unusually high white blood cell counts.
- Coho salmon engineered for transgenic expression of growth hormone were more aggressive predators in simulated natural environments.
- Transgenic coho salmon expressing growth hormone had enlarged heads, reduced viability, and accelerated development of their life cycle.
- Transgenic expression of growth hormone in coho salmon led to a narrower body, more red muscle mass, and smaller white muscle fibers.
- Atlantic Salmon expressing transgenic growth hormone experienced numerous changes to their cardiorespiratory system.

The widespread, unpredictable side effects found in genetically engineered organisms constitute one of the most under-reported news stories of our day, especially in America. You can help remedy this by pointing others—including journalists, policymakers, and interested citizens—to nontarget.org.

Transgenic (GM) salmon have been genetically altered so as to produce more growth hormone in their bodies. Both the transgenic and non-GM wild fish pictured here were raised in laboratories. The transgenic salmon hatched 2 to 3 days earlier than the non-GM fish. All the fish were fed commercial salmon feed to satiation, and the transgenic salmon grew and developed much more rapidly. At 6 months the transgenic salmon changed to a silvery color (smolt stage), which typically occurs by 2 years of age in non-GM salmon raised in hatcheries. They were sexually mature at 2 years in comparison to 3-4 years in hatchery-raised non-GM salmon. Overall the transgenic fish had slightly paler coloration throughout life and also had larger heads and gill coverings than normal salmon. In addition, there was a lower survival rate in the transgenic salmon ("reduced viability"). (Scale bars: 10 cm.; drawings by C. Holdrege after photographs in: Devlin, R. H., C. A. Biagi, T. Y. Yesaki (2004). "Growth, Viability, and Genetic Characteristics of GH Transgenic Coho Salmon Strains," *Aquaculture* vol. 236, pp. 607-32.)

The Aqua Bounty company has been trying since 1996 to get its genetically engineered "AquaAdvantage" fast-growing fish (salmon, tilapia, and trout) approved by the Food and Drug Administration for commercial sale. Due to concerns about safety, reliability of the genetic modification, and environmental impact (potential for escape into the wild and hybridization with wild salmon), this approval has not yet been given.



Events at The Nature Institute

Here's some of what's been happening, and will be happening, at The Nature Institute:

Upcoming Events

Depending on when you receive this newsletter, the following events may still be forthcoming:

** "Regenerative Land Practices in Colombia and Brazil," a talk and slide presentation by Justin West (Friday, May 7, 7:30 pm).

The degradation of land and the loss of biodiversity due to human practices are deeply troubling. But there are also inspiring examples of how people can mitigate ecological unraveling and loss of biodiversity by weaving principles of ecology and diversity into the food- and fuel-producing agroecosystems themselves. In 2009, agroecologist Justin West visited Colombia and Brazil, and he will present a photographic journal of some of the most impressive, inspiring, and encouraging food and agroforestry systems being designed in the tropics today.

** Edible Mushroom Cultivation Workshop, with Justin West (Saturday, May 8, from 9 a.m. to noon).

This is a hands-on workshop covering shiitake mushroom cultivation on logs. Justin will discuss various techniques for home-scale cultivation of mushrooms. Participants will inoculate hardwood logs with shiitake spawn which later will yield mushrooms.

** Monday Nights with the Stars, with Henrike Holdrege (March 22, April 12, May 10 at 8:00 pm).

This spring Henrike Holdrege is offering evenings of night sky observation. The sessions focus on the movements and rhythms of Sun and Moon. When the sky is not clear, we work indoors.

Past Events

** A group of Nature Institute staff, board members, and friends came together on an April weekend to discuss "The Nature Institute: Past, Present, and Future." This colloquium provided the opportunity to reflect on the Institute's founding impulse and what we have achieved in the time since the Institute was founded in 1998. Based on these

considerations we began a conversation — which will continue — about future directions.

** On Earth Day (April 22) Craig gave a talk entitled "Thinking Like a Mountain," dealing with the future of the earth and the legacy of Aldo Leopold. Leopold was one of the most significant ecologists and ecological thinkers of the twentieth century. He believed that human beings could develop a way of thinking and being in the world — he called it "thinking like a mountain" — that would enable humanity to play a more integrated role in the whole of nature. Craig developed this key idea within the context of Leopold's life and times, and showed its relevance for our own day.

** "Plants, Earth, and Cosmos" — 2010 winter intensive course for farmers, gardeners, and apprentices from around the country. Attendees of the week-long course in February, whose ages ranged from 20 to 60, had a wide variety of experiences in farming and gardening. It was an engaging group of people to work with, and the coming together of young and old, experienced and inexperienced, brought much fruitful interaction. The course was a real joy to be part of.

Our main aim in the course was to introduce participants to the phenomenological way of seeing nature, as well as to stretch their thinking through projective geometry. The work centered on plant studies and astronomy. One young farm apprentice remarked afterward, "I feel the course was a very interesting progression of ideas and questions. I think I can confidently say that I have the beginnings of a new perspective on the formation of plants and a new methodology with



Participants in the 2010 winter intensive course, "Plants, Earth, and Cosmos."

which to observe the natural world.” An experienced farmer wrote in her evaluation about the astronomy segment of the course, “There were a lot of connections made for me that I have struggled with in my studies of astronomy over the years.”

Seven of the participants transitioned from the week at The Nature Institute to a week of lectures and presentations at Hawthorne Valley Farm Learning Center, where they learned about biodynamic farming and sustainable practices in farming and gardening. The two intensives were planned in conjunction with each other so that apprentices participating in the North American biodynamic farming apprenticeship program could attend both weeks.

Out and About

April saw Craig traveling in California:

** He gave a presentation on observation and dynamic thinking at RSF Social Finance in San Francisco.

** At the San Francisco Waldorf School he spoke to parents and teachers on “Tending the Roots of Sustainability: Education for the Future of Children and the Earth.” There he developed in some new directions the theme he had introduced during a January conference at the same school. He also gave a talk to the high school students on genetically modified food.

** Finally, he spent three days at a conference held by the Kalliopeia Foundation called “Emergence.” It brought together individuals from the organizations the foundation supports and partners with. It was a remarkable event. The foundation tends to support small organizations that have some kind of spiritual orientation through which they bring deeper and unified perspectives to concrete problems in the world. Individuals gave presentations out of their lives and work and there were many smaller group sessions. Many important meetings took place at meal times. For Craig it was a deeply moving experience to meet so many different kinds of people working in a great variety of fields, and nonetheless to feel there is an underlying common striving.

In March Steve participated in a conference on synthetic biology at the Hastings Center in the lower Hudson Valley of New York. Synthetic biology is, you might say, a more ambitious sibling of genetic engineering. Its a discipline where one attempts to synthesize new organisms in whole or in part. The conference at the Hastings Center was one of a series of three aimed at gaining an understanding of the new discipline, especially from an ethical point of view. Partici-

pants included molecular biologists working on synthetic biology, philosophers, and social scientists, among others.

In his own talk, Steve pointed to the “vastly underappreciated implosion of the gene-centered model of the organism,” and then spent the bulk of his time sketching the implications of current molecular biological findings for the character of the organism and the nature of biological explanation. Everything, he suggested, is leading us back toward the organism as an integrated and unified whole without which we cannot understand the parts. We are being nudged toward a reconsideration of the long-neglected notion that the organism is first of all a *being*, not a thing or machine.

The conversation following the talk was extraordinarily vigorous and intense — and (for Steve, anyway!) extremely satisfying. Afterwards one of the other speakers remarked to him, “I think you rattled some cages.” A follow-up conference at the Hastings Center, which Steve also expects to attend, will be held in May. For a commentary on the March conference, see *NetFuture* #180 (http://netfuture.org/2010/Mar2510_180.html).

Here, briefly, are some of our other activities:

** In January Craig gave a keynote lecture on “Tending the Roots of Sustainability: Education for the Future of Children and the Earth” at the Annual Conference of Public Waldorf Schools at Rudolf Steiner College in Fair Oaks, California. The conference was attended by about two hundred teachers, administrators, and board members. Craig also held a workshop on dynamic thinking through plant study.

** Also in January, Henrike gave three afternoon sessions on teaching middle school geometry for teachers at the Meadowbrook Waldorf School in Rhode Island.

**In April Craig gave an afternoon workshop at the biodynamic gardening and farming course at the Pfeiffer Center in Chestnut Ridge, New York. He addressed the question, How can we gain a qualitative understanding of plants and animals? He also spoke about our modern human dilemma that we are, in consciousness, cut off from a deeper relation to nature. As a path to bridge this gulf, Goethean phenomenology allows us to participate in the living and dynamic qualities of nature. In this way, the study of plants and animals becomes a means of re-rooting ourselves in the world. It also provides the foundation for responsible human action, for example in farming, because we can begin to take the deeper nature of plants and animals into account in the way a farm operation is developed.

Thank You !

Our heart-felt thanks go out to all of you who have contributed money, services, or goods
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(continued on p. 19)

Context Matters — the Epigenetics Revolution

Steve Talbott

Following are three excerpts from a series of lengthy articles entitled “On Making the Genome Whole,” available at <http://natureinstitute.org/txt/st/mqual>. The excerpts are intended to provide an introduction to the new molecular biological researches that are causing a thorough implosion of the old, gene-centered understanding of the organism. References have been removed from the text here and may be found in the original articles, as indicated in the note at the end.

I Lusting for a Code

WHEN IT EMERGED A FEW YEARS AGO that humans and chimpanzees shared, by some measures, 98 or 99 percent of their DNA, a good deal of verbal hand-wringing and chest-beating ensued. How could we hold our heads up with high-browed, post-simian dignity when, as the *New Scientist* reported, “chimps are human”? If the DNA of the two species is more or less the same, and if, as nearly everyone seemed to believe, DNA is destiny, what remained to make us special?

Such was the fretting on the human side, anyway. To be truthful, the chimps didn’t seem much interested. And their disinterest, it turns out, was far more fitting than our angst.

In 1992 Nobel prizewinning geneticist Walter Gilbert wrote that you and I will hold up a CD containing our DNA sequence and say, “Here is a human being; it’s me!” His essay was entitled, “A Vision of the Grail.” Today one can only wonder how we became so invested in the almost sacred importance of an abstract and one-dimensional *genetic code* — a code so thinly connected to the full-fleshed reality of our selves that its entire import could be captured in a naked and scarcely coherent string of four endlessly repeating letters, like so:

ATGCGATCTGTGAGCCGAGTCTTTAAGTTC

It’s true that the code, as it was understood at the height of the genomic era, had *some* grounding in material reality. Each of the four different letters represented one of the four nucleotide bases constituting the DNA sequence. And each group of three successive letters (referred to as a *codon*)

potentially represented an amino acid, a constituent of protein. The idea was that the bases in a protein-coding DNA sequence, or gene, led to the synthesis of the corresponding sequence of amino acids in a protein. And proteins play a decisive role in virtually all living processes. By specifying the production of proteins, genes were presumed bearers of the blueprint, or master program, or molecular instruction book of our lives.

Certainly the idea seemed powerful to those who were enamored of it. In their enthusiasm they gave us countless cellular *mechanisms* and one revolutionary gene discovery after another — a gene for cancer, a gene for cystic fibrosis (excerpted above), a gene for obesity, a gene for depression, a gene for alcoholism, a gene for sexual preference . . . Building block by building block, genetics was going to show how a healthy human being could be constructed from mindless, indifferent matter.

And yet the most striking thing about the genomic revolution is that the revolution never happened. Yes, it’s been an era of the most amazing technical achievement, marked by an overwhelming flood of new data. Supposed new molecular mechanisms are being detailed weekly. But one might easily think that the meaning of it all — how we can understand the integrity and unified functioning of the living cell — has been more obscured than illumined by the torrent of data. It’s true that we are gaining, even if largely by trial and error, certain manipulative powers. But what about our clouded vision of the Grail? “Many of us in the genetics community,” write Linda and Edward McCabe, authors of *DNA: Promise and Peril*, “sincerely believed that DNA analysis would provide us with a molecular crystal ball that would allow us to know quite accurately the clinical futures of our individual patients.” Unfortunately, as they and many others now acknowledge, the reality did not prove so straightforward.

As minor tokens of the changing consciousness among biologists, one could cite articles from this past year in the world’s two premier scientific journals, each reflecting upon the discovery of the “gene for cystic fibrosis.” THE PROMISE OF A CURE: 20 YEARS AND COUNTING — so ran the headline in *Science*, followed by this slightly sarcastic gloss: “The discovery of the cystic fibrosis gene brought big hopes for gene-based medicine; although a lot has been achieved over two decades, the payoff remains just around the corner.”

An echo quickly came from *Nature*, without the sarcasm: ONE GENE, TWENTY YEARS — “When the cystic fibrosis gene was found in 1989, therapy seemed around the corner. Two decades on, biologists still have a long way to go.”

The story has been repeated for one gene after another, which may be part of the reason why molecular biologist Tom Misteli offered such a startling postscript to the unbounded optimism of the Human Genome Project. “Comparative genome analysis and large-scale mapping of genome features,” he wrote in the journal *Cell*, “shed little light onto the Holy Grail of genome biology, namely the question of how genomes actually work” in living organisms.

But is this surprising? The human body is not a mere implication of clean logical code in abstract conceptual space, but rather a play of complexly shaped and intricately interacting substances and forces. Yet the four genetic letters, in the researcher’s mind, became curiously detached from their material matrix, with its complexities of resistant form and muscular action. Given the way many discussions were pursued, it hardly would have mattered whether the letters of the “Book of Life” represented nucleotide bases or completely different molecular combinations. All that counted were certain logical correspondences between code and protein together with a few bits of regulatory logic — all but-tressed, to be sure, by the massive weight of an unsupported assumption: somehow, by neatly executing our dematerialized formulation of its supposedly computer-like DNA logic, the organism would fulfill its destiny as a living creature. The details could be worked out later. That the *enlivened physical being* of the gene and chromosome must have more to contend with, and more to contribute, than obedience to a one-dimensional code marking out an immaculate causal connection linking DNA and protein — this certainty didn’t seem to burden many geneticists unduly.

The misdirection in all this badly needs elaborating — a task I hope to advance here. As for the differences between humans and chimpanzees, the only wonder is that so many were exercised by it. If we had wanted to compare ourselves to chimps, we could have done the obvious and direct and scientifically respectable thing: we could have observed ourselves and chimps, noting the similarities and differences. Not such a strange notion, really — unless one is so transfixed by a code abstracted from human and chimp that one comes to prefer it to the organisms themselves — the organisms that are the only possible source for whatever legitimacy and physical meaning the abstraction possesses.

I’m not aware of any pundit who, brought back to reality from the realm of code-fixated cerebration, would have been so confused about the genetic comparison as to invite a chimp home for dinner to discuss world politics. If we had

been looking to ground our levitated theory in scientific observation, we would have known that the proper response to the code similarity in humans and chimps was: “Well, so much for the central, determining role we’ve been assigning to our genes.”

Thankfully, that seems to be where biology is getting to these days. We are progressing into a post-genomic era — often referred to as the era of *epigenetics*.

II

Reckoning with the Environment

“Epigenetics” most commonly refers to heritable changes in gene activity associated with factors other than the actual DNA sequence of the genes. But in order to understand the important developments now under way in biology, it’s more useful to take “epigenetics” in its broadest sense as “putting the gene in its living context”.

In the mammalian genome chromosomes normally come in pairs, one inherited from the mother and the other from the father. Any given gene occurs twice, with one version (“allele”) located on the first chromosome of a pair and the other on the second. When the two alleles are identical, the organism is said to be *homozygous* for that gene; when the alleles are different, the organism is *heterozygous*. For example, there are mice that, in their natural (“wildtype”) state, are dark-colored — a color that is partly dependent on a gene known as *Kit*. The mice are normally homozygous for this gene. When, however, one of the *Kit* alleles is replaced with a certain mutant gene, the now heterozygous mouse shows white feet and a white tail tip.

That result was perfectly natural (if you call such artificial gene manipulations “natural”). But it is also where the story becomes interesting. Scientists at the University of Nice-Sophia Antipolis in France took some of the mutant, white-spotted mice and bred them together. In the normal course of things, some of the offspring were again wildtype homozygous animals — neither of their *Kit* alleles was mutant. However, to the researchers’ surprise, these “normal,” wildtype offspring maintained, to a variable extent, the same white spots characteristic of the mutants. It was an apparent violation of Mendel’s law of inheritance: while the genes themselves were sorted between generations properly, their effects did not follow the “rules.” A trait was displayed despite the absence of its corresponding gene. Apparently something in addition to the genes themselves — something epigenetic — figured in the inheritance of the mice offspring, producing the distinctive coloration.

Another group of researchers, led by Michael Skinner at the University of Washington, looked at the effects of the fungicide vinclozolin on laboratory rats. Banned in Scandinavia and Europe but allowed on some crops in the U.S., vinclozolin is an endocrine-disrupting chemical. If pregnant female rats are exposed to it while their embryos are undergoing sexual organ differentiation, the male offspring develop serious problems as adults — death of sperm-generating cells, lowered sperm count and motility and, later, immune abnormalities and various diseases including cancer. The remarkable thing is that the effects, which were not rooted in changes to the DNA sequence, were found to be transmitted over four generations without weakening. That is, acquired characteristics — deficiencies in embryos brought on by fungicide exposure — were inherited by offspring who were not subject to the same exposure. This led Skinner to ask a troubling question: “How much of the disease we see in our society today is transgenerational and more due to exposures early in life than anything else?”

The whole business looks rather like vindication for the long-dismissed Lamarckian doctrine of the inheritance of acquired characteristics, a doctrine that has indeed been making a comeback of late. But inheritance aside, puzzling results such as these put the question, “Are genes equivalent to destiny?” in a new light. In 2007 a team of researchers at Duke University reported that exposure of pregnant mice to bisphenol A (a chemical used in many common plastics such as baby bottles and dental composites) “is associated [in the offspring], with higher body weight, increased breast and prostate cancer, and altered reproductive function.” The exposure also shifted the coat color of the mice toward yellow — a change again found to be transmitted across generations despite its not being linked to a gene mutation. But more to the present point: the changes brought on by the chemical were negated when the researchers supplemented the maternal diet with folic acid, a B vitamin.

And so the “epigenome” — everything in the cell that bears on gene expression — responds to healthy as well as unhealthy influences. As another illustration of this: researchers at McGill University in Montreal looked at the consequences of two kinds of maternal behavior in rats. Some mother rats patiently lick and groom their newborns, while others generally neglect their pups. The difference turns out to be reflected in the lives of the offspring: those who are licked grow up (by the usual measures) to be relatively confident and content, whereas the neglected ones show depression-like symptoms and tend to be fearful when placed in new situations.

This difference is correlated with different levels of activity in particular genes in the hippocampus of the rats’

brains. Not that the genes themselves are changed; the researchers found instead that various epigenetic modifications of the hippocampus alter the way the genes work. Other investigations have pointed toward similar changes in the brains of human suicide victims who were abused as children.

Perhaps even more surprisingly, mouse embryos grown by means of in vitro fertilization (IVF) — spending their first several days in a petri dish — showed epigenetic changes resulting in altered gene activity. And now there are reports that humans conceived through IVF have an increased risk of several birth defects. The main suspect is again the epigenome.

III Paradoxes

To realize the full significance of the truth so often remarked in the technical literature today — namely, that context matters — is indeed to embark upon a revolutionary adventure. It means reversing one of the most deeply engrained habits within science — the habit of explaining the whole as the result of its parts. If an organic context really does rule its parts in the way molecular biologists are beginning to recognize, then we have to learn to *speak* about that peculiar form of governance, turning our usual causal explanations upside down. We have to learn to explain the part as an expression of a larger, contextual unity.

Historically, an intellectual recoiling from this necessity was what led to an overly narrow concept of the genetic code. The code was supposed to reassure us that something like a computational machine lay beneath the life of the organism. The fixity, precision, and unambiguous logical relations of the code seemed to guarantee its strictly mechanistic performance in the cell. Yet it is this fixity, this notion of a precisely characterizable march from cause to effect — from gene to trait — that has lately been dissolving more and more into the fluid, dynamic exchange of living processes. Organisms, it appears, must be understood and explained at least in part from above downward, from context to subcontext, from the general laws or character of their being to the never fully independent details. In the end, we can meaningfully apprehend the lowest-level activities only so far as we recognize them to be performances of the whole organism.

A number of apparent paradoxes helped to nudge the molecular biologist toward a more contextualized understanding of the gene. To begin with, the Human Genome

Project revised the human gene count downward from 100,000 to somewhere between 20-25,000. What made the figure startling was the fact that much simpler creatures — for example, a tiny, transparent roundworm — were found to have roughly the same number of genes. More recently researchers have turned up a pea aphid with 34,600 genes and a water flea with 39,000 genes. If genes account for our complexity and make us what we are — well, not even the “chimps are human” advocates were ready to set themselves on the same scale with a water flea. The difference in gene counts required some sort of shift in our understanding.

A second oddity centered on the fact that, upon “deciphering” the Book of Life, we found that our coding scheme made the vast bulk of it read like nonsense. That is, some 95 or 98 percent of human DNA was not a carrier of the genetic code at all. It was useless for making proteins. Most of this *noncoding DNA* was at first dismissed as “junk” — meaningless evolutionary detritus accumulated over the ages. At best it was viewed as a kind of bag of spare parts, borne by cells from one generation to another for possible employment in future genomic innovations. But that’s an awful amount of junk for a cell to have to lug around, duplicate at every cell division, and otherwise manage on a continuing basis.

Another paradox — perhaps the most decisive one — was recognized and wrestled with (and more often just ignored) going back to the early twentieth century. With few exceptions, every different type of cell in the human body contains the same chromosomes and the same DNA sequence as the original, single-celled zygote. Yet somehow this zygote manages to differentiate into every manner of tissue — liver, skin, muscle, brain, blood, bone, retina . . . If genes determine the form and substance of the organism, how is it that such radically different cellular architectures result from the same genes? What directs genes in their temporally and spatially varying activity so as to produce the intricately sculpted and complexly differentiated form of a human being? And how can this directing agency be *governed* by the very genes it directs?

The developmental biologist F. R. Lillie, remarking in 1927 on the contrast between “genes which remain the same throughout life” and a developmental process that “never stands still from germ to old age,” asserted that “Those who desire to make genetics the basis of physiology of development will have to explain how an unchanging complex can direct the course of an ordered developmental stream.”

Think for a moment about this ordered developmental stream. When a cell of the body divides, the daughter cells can be thought of as “inheriting” traits from the parent cell. The puzzle about this cellular-level inheritance is that, especially during the main period of an organism’s development,

it leads to a dramatic, highly directed differentiation of tissues. For example, embryonic cells on a path leading to heart muscle tissue become progressively more specialized. The changes each step of the way are “remembered” (that is, inherited) — but what is remembered is caught up within a process of continuous change. You cannot say that “every cell reproduces after its own likeness.”

Over successive generations, cells destined to become a particular type lose their ability to be transformed into any other tissue type. And so the path of differentiation leads from *totipotency* (the single-celled zygote is capable of developing into every cell of the body), to *pluripotency* (embryonic stem cells can transform themselves into many, but not all, tissue types during fetal development), to *multipotency* (blood stem cells can yield red cells, white cells, and platelets), to the final, fully differentiated cell of a particular tissue. In tissues where cell division continues further, the inheritance thereafter may take on a much greater constancy, with like giving rise (at least approximately) to like.

Cells of the mature heart and brain, then, have inherited entirely different destinies, but the difference in those destinies was not written in their DNA sequences, which remain identical in both organs. If we were stuck in the “chimp equals human” mindset, we would have to say that the brain is the same as the heart.

So what’s going on? The paradoxes mentioned above turn out to be intimately related. One strong hint pointing toward their resolution lay in the fact that, as organisms rise on the evolutionary scale, they tend to have more “junk DNA.” Noncoding DNA accounts for some 10% of the genome in many one-celled organisms, 75% in roundworms, and 98% in humans. The ironic suspicion quickly became too obvious to ignore: maybe it’s precisely our “junk” that differentiates us from water fleas. Maybe what counts most is not so much the genes themselves as the way they are regulated by the larger context. Noncoding DNA could provide the complex regulatory functions that direct genes toward service of the organism’s needs.

That suspicion has now become standard doctrine — a still much-too-simplistic doctrine, if one stops there, however. For noncoding as well as coding DNA sequences continue unchanged throughout the organism’s entire trajectory of differentiation, from single cell to maturity. Lillie’s point therefore remains: it is hardly possible for an unchanging complex to explain an ordered developmental stream. *Things* cannot by themselves explain *processes*.

We need a more living understanding. It is not only that

noncoding DNA is by itself inadequate to regulate genes. What we are finding is that at the molecular level the organism is so dynamic, so densely woven and multidirectional in its causes and effects, that it cannot be explicated as living process through *any* strictly local investigations. When it begins to appear that “everything does everything to everything,” as one pair of researchers put it in the journal *Cellular Signalling*, the search for “regulatory control” necessarily leads to the unified and irreducible functioning of the cell and organism as a whole.

Concluding Remarks

The actual epigenetic discoveries of the past decade or so, many of which are reviewed in the full-length articles from which the foregoing excerpts were lifted, are far too complex to try to summarize in a brief space. In fact, complexity and subtlety, as indicated by ubiquitously employed terms such as “regulation,” “coordination,” “control,” “integration,” “plasticity,” “contextuality,” and many others, is almost the whole point of the new discoveries. Except that the regulation can no longer be conceived as issuing from some master controlling molecules such as DNA; rather, it is a function of the organism as a whole, working always in a direction from context to subcontext, from whole to part.

The collapse of the gene-centered model for understanding the organism — the loss of the gene as First Cause and Unmoved Mover — is a truly revolutionary shift in the foundations of biology. The growing (if still not fully welcome) sense among researchers that fundamental changes are afoot results in an occasional remark like this one by molecular biologist Toby Gibson in *Trends in Biochemical Sciences*:

There is no dictator in cell regulation, no first among equals, no master regulator, no top-down system of governance. The time has come to acknowledge that the cell is anarcho-syndicalist...

I don't know about “anarcho-syndicalist.” What I do know is that the cell manages to live in harmony with itself and with the larger organismic context. Discovering how to think about this harmony of the whole organism without appealing to some sort of master blueprint or instruction book will be the challenge biologists face as the full implications of the epigenetic revolution come into clearer focus.

REFERENCES

For references to sections I and III above, please see Part 4 of “On Making the Genome Whole,” available at <http://nature-institute.org/txt/st/mqual>. For references to section II, see Part 1 of the same series.

Thank You ! (continued from p. 14)

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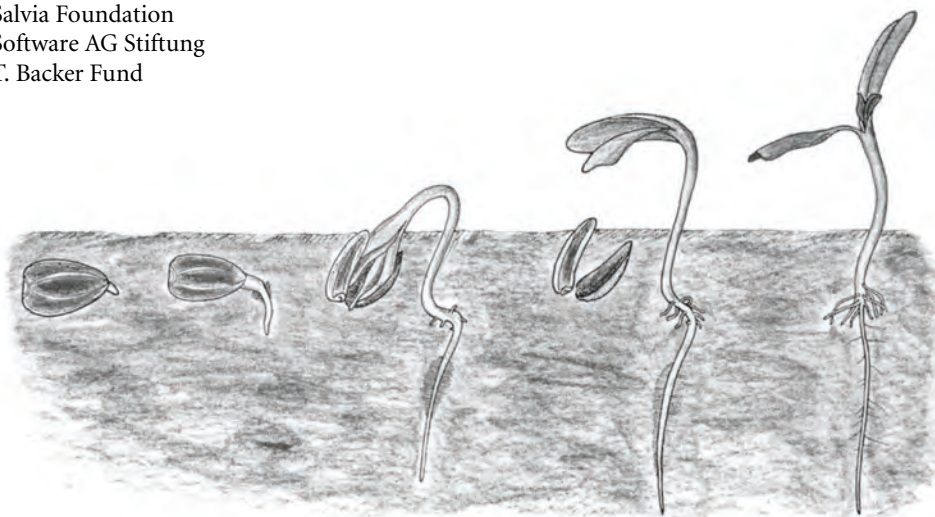
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