Three

The Engine of Transformation

> We have...no convincing account of evolutionary progress--of the otherwise inexplicable tendency of organisms to adopt ever more complicated solutions to the problems of remaining alive.
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> Peter B. Medawar

> Theories are like nets: only he who casts will catch.
>
> Novalis

Now I will classify all animal genes that ever existed into four groups based on their historical relationship with cancer.

Oncogenes, which I have already described, comprise the first group. According to my theory, oncogenes have always been inside all somatic cells of organisms created by the animal lineages.

Genes in the second classification are called *anti-oncogenes*. These are defined as genes that were initially selected because they reduced genetic losses to lethal cancer; they're genes for the cancer defenses described in the last chapter. As I demonstrated in Black Box Exercise II, all cancer defenses and therefore *all anti-oncogenes functioned also as enhancers of precise replication of the genetic program during the cell-by-cell development of the animal*. That conclusion enables me to make an important extension of the theory:

Increases in selection pressure from cancer led to increases in the ability to create animals of complexity. The more lethal juvenile cancer a lineage experienced, the more anti-oncogenes--the enablers of complexity--it accumulated.

(The direct correlation between the intensity of selection pressure, from whatever cause, and the degree of the response to that pressure has long been observed in nature. A good example is the speed of cheetahs, who have been clocked at ninety miles per hour, and the ability of newborn African antelopes to run minutes after they are dropped by their mothers. Many cheetahs had to die of starvation and many clumsy newborn antelopes were had to be killed in order for those remarkable abilities to have emerged. There are many other obvious examples of animal characteristics, including the extraordinary camouflage of many insects, which could not have come into existence unless selection pressure--intense and prolonged pressure--favored their origin.)

Molecular biologists have identified functional anti-oncogenes inside the cells of modern animals. However, my definition of anti-oncogenes is a historical one and it differs significantly from what molecular biologists mean when they use the term. Those researchers only consider as anti-oncogenes those genes that serve that function *now*, inside the cells of modern animals, as determined by experimental research. (They frequently call them tumor suppressors.)

As understandable and appropriate as that approach may be to cancer researchers, I need to look at cancer defenses differently. I am not trying to identify existing cellular defenses against cancer. Rather, I am constructing a theory to explain 800 million years* of animal evolution in millions of different lineages. Because I have a different objective, most

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Most works I've consulted place the origin of animals at between 600 and 700 million years ago. James W. Valentine, who says fossils can only give us an estimate for the origin of animal life, mentions a range of from 750 to 1,200 million years ago. The figure I use, 800 million ago, is further back than many estimates, but if I am wrong and animal evolution began later--or sooner--so be it. The precise date is as unimportant as it is unknowable.

of my anti-oncogenes would not be considered anti-oncogenic by molecular biologists. I consider genes, for example, for the construction of noncellular external coverings of animals (the shells of sea turtles, the exoskeletons of insects, etc.) to be anti-oncogenes. They were selected because (1) they prevented genetic deaths from cancer by protecting the dividing cells of the animal from exposure to sunlight and, possibly, other natural radiation and (2) many animals without them died of cancer.

All animal lineages, having endured significant genetic losses to mutagen-induced cancer in juveniles, now possess a powerful array of anti-oncogenes. The reason those germ lines produce animals of exquisite complexity lies in the abundance of anti-oncogenes--everyone of them development-enhancive--that were collected because the lineages endured losses from cancer. Because of their abundance, variety and great importance--without them animals would not exist--I comment further on specific anti-oncogenes in future chapters.

The third group of genes are those that answer a question that may have already occurred to some readers (as it did to *The Economist*). If cancer came into existence 800 million years ago, why didn't selection eliminate it, at least as a killer of *young* animals? Wouldn't the selection of increasingly efficacious anti-oncogenes--defenses against cancer--have led to the elimination of the disease in juveniles? The answer to those questions is--Well, yes, certainly. *If* the old theory were correct that's precisely what would have happened. Selection would have long ago extinguished cancer's ability to kill young animals. Unfortunately for old theory advocates however, what it predicts ought to have happened did *not* happen.

Unlike the old theory, mine is correct. It states that cancer in juveniles would have been eliminated in a lineage, only if the lineage kept replicating the same basic animal over and over again, for many millions of years--in other words, if evolution in that lineage stopped. As we shall see, there are some modern animals--evolutionary dead ends--that have extremely low cancer rates for precisely that reason. But most animal lineages did not produce the same animal throughout geologic time in a never-ending stream of generations. Changes occurred. Evolution happened.

Many lineages created increasingly complex animals, and *that* is why juvenile cancer occurs hundreds of millions of years after its origin.

To explain further, imagine an animal lineage that has been producing the same organism for a very long time. Because cancer selection has been steadily eliminating inefficient genes (those incapable of performing the process of development with great precision), the efficiency of the DNA in the germ line is now extremely high; the morbid process initiated by failure to replicate efficiently--cancer--has become rare among juveniles. Now let us suppose that a series of beneficial germ line mutations are inserted into the lineage's gene pool. Imagine also that the environment changes in a way that most animals without the characters called for by those recent mutations are eliminated. The lineage would very quickly start producing animals that were significantly different from those that it had been producing. What would happen to the rate of cancer under those circumstances?

According to my theory, and to logic, the rate of cancer would *increase*, concurrent with the introduction of the new adaptive character. It is contrary to logical expectations that the new-model animals could be produced with the same level of efficiency as the old models. The genes for the introduction of new characters were adaptive--they enabled more animals to survive--but they also increased cancer rates. They were both adaptive and pro-oncogenic.

But how could these *adaptive pro-oncogenes*, genes that actually *increased* cancer death rates, have been selected? Isn't *that* contrary to logical expectation? Not at all. In order to be selected, all the new genes had to do was to increase the *net* survival rate of animals equipped with them to a level higher than that of animals without the new genes.

Let's look at a hypothetical illustration to see how that would work. Assume that OLD character in a lineage has recently been significantly improved through the introduction of a germ line mutation. The mutation creates the improved model which I call NEW character. I have summarized the hypothetical survival rates (deliberately exaggerated for explanatory purposes) of animals with NEW character compared with OLD character in the following table:

Death Rate Among Juveniles

Animals with	Caused By Cancer	Other	Total	Survivors
OLD character	1%	89%	90%	10%
NEW character	10%	35%	45%	55%

NEW character animals would out-survive OLD character animals by a factor of five-and-one-half to one (55% to 10%). In just a few generations, NEW character would be in and OLD character would be out. But despite its obvious survival benefits the inevitable selection of NEW character would bring with it a *ten-fold increase* in cancer death rates.

Gene pools, like hard-nosed entrepreneurs, are interested only in the bottom line. The *net* survival benefit of NEW character ensures that it replaced OLD character. And replacement would be swift. Although I have used exaggerated numbers, actual selection worked on much smaller differentials; geneticists have determined that if a mutation provides a mere 1% survival benefit it will conquer a population in about 100 generations.

Recent findings by molecular biologists support the idea that increases in complexity were accompanied by increases in cancer death rates. That research (summarized in Chapter Eleven) suggests that the more highly transformed lineages have collected more oncogenes than less evolved ones. Selection of some genes, or families of genes, for complexity apparently involved selection of more genes for rapid growth (of a larger body or a new organ, perhaps). These new genes could have acted like the original oncogenes: active in the early stages of embryogenesis and then deactivated (by anti-oncogenes), unless a mutagenic event turned them loose with fatal consequences.

But whether or not new oncogenes were added as complexity

increased is not essential to this part of the theory. What is essential is that new molecular complexities added to the informational load transferred from mother cell to daughter cells during mitosis. Increases in mitotic complexity increased the likelihood of errors and the initiation of cancer.

Cancer caused by the selection of innovations would have occurred *even if the newly selected character was itself cancer-defensive.* This seemingly paradoxical situation is actually observable in humans. Both our lymph systems and our white blood cells play important roles in fighting cancer. However, lethal lymphoma (cancer of lymph cells) and leukemia (cancer of white blood cells) are a fact of life (and of death): cancer can occur in organs that fight cancer.* So it would have been for any genes that were historically selected for cancer protection. The unavoidable increase in the replication load borne by the dividing cells would have increased the possibility of carcinogenic errors in mitosis.

Because of its crucial nature, I will now offer an additional argument in favor of the idea that increases in complexity caused increases in cancer deaths among juvenile animals.

As has been the case in the past, products of human intelligence can help us to understand natural phenomena. Others have pointed out that man's invention of the mechanical pump helped him to understanding how the heart works. Similarly, our understanding of the nervous system was facilitated by man's invention of electric distribution systems and wire-based communication networks. More recently, computers have helped us to understand how the brain works.

Just as those and other comparisons of body organs and organ systems

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The same peculiar relationship exists in man-made cancer treatments. Radiation can both initiate cancer and kill cancer cells. This phenomenon helped me to conclude that all cells contain cancer triggers--before the molecular biologists discovered them:

Cancer cells could either die or survive when exposed to radiation, but they could not become what they already were: cancerous. Normal cells had more choices. In addition to surviving or dying they could be transformed to the cancerous state; ergo, they had within them the capacity to become cancerous. They had cancer triggers; they had oncogenes.

to man-made, multi-part machines have proven helpful to biology, man's experience in *manufacturing* great numbers of complicated objects ought to help us to understand biological evolution. In fact an excellent, well-documented record of specific experience helps us enormously. It occurred in the aircraft industry.

During World War II American manufacturers noticed that as they mass-produced a particular airplane in the great numbers demanded by the war effort, the efficacy of the process improved dramatically. As the cumulative numbers of finished aircraft increased the total worker-hours needed to manufacture each plane decreased.

Significantly, the manufacturers also noticed that if major modifications were introduced in the design of the aircraft, efficiency dropped and the number of worker-hours needed to complete each plane went up. Then, once employees became familiar with the new version, costs again trended downward.

The manufacturers eventually realized that this phenomenon--which is now called the *manufacturing progress function* or the *learning curve*--was constant and predictable. They learned to forecast with mathematical certainty the decreases in manufacturing costs that followed the introduction of a new model.

Engineers in other industries learned that the same concept applied to their products: the initial high cost (the direct result of low efficiency) of manufacturing new products always decreased over time. The underlying reasons for that are clear and commonsensical. New models required workers to learn new procedures. Not being familiar with the new steps, mistakes were made and efficiency dropped below previous levels. But the repetitive nature of mass manufacturing ensured that the workers would eventually master the new steps, make fewer errors and increase efficiency. Learning curves work.

Now if the learning curve phenomenon prevails in human-controlled manufacturing--as common sense tells us it would--on what grounds can we *assume* that a similar phenomenon was absent in biological evolution? Shouldn't prudent theorists presume that the aggregate of DNA in a lineage at first found it more difficult to produce newly revised versions

of organisms? And that efficiency increased over time? But if a learning curve did operate during biological evolution how did it function? How did dumb, blind genes learn to manufacture, with extremely low error rates, extraordinarily complex objects?

There is only one plausible answer. Lineages could have climbed evolution's learning curve only if genes that committed errors in construction were eliminated. And the only way genetic material responsible for mistakes that occurred in the replication of molecules inside the nuclei of individual cells could be eliminated is if that imperfection caused the prompt death of the animal and all of its genes. The *only* known means for a replication error inside a cell to kill a developing animal is the process we call cancer.

I have described adaptive pro-oncogenes as genes that added to the complexity of the animal in the form of a new or improved character. Actually, many other adaptive changes would have increased cancer selection pressure. We know, for example, that modern humans and the other terrestrial vertebrates live in a sunnier, more naturally mutagenic-carcinogenic, habitat than our marine ancestors. We also know that modern humans are bigger and live longer juvenile lives than the earliest mammals. Newly selected genes that enabled those changes to be expressed would have increased cancer death rates following selection.

Further support for the idea that genes for the introduction of adaptive characters caused new waves of cancer is found in modern cancer statistics for children. I comment on them in Chapter Eleven.

Having, I hope, destroyed all resistance to the idea that past increases in organism complexity caused increases in the intensity of cancer selection, I must take care not to oversimplify. Some anti-oncogenes enabled *future* increases in complexity. Genes that provided (for example) whole body protection against solar radiation would function for hundreds of millions

of years; new mutations entering the gene pool long after the shield was in place would benefit from its protection.

My theory, in other words, does not insist that *all* changes in complexity were invariably followed by increases in cancer. Which brings me to the fourth group of animal genes: *cancer-neutral genes*. These are genes whose selection was followed by neither an in-crease nor a decrease in cancer rates following their selection.

To sum up, the three kinds of cancer-related animal genes involved in transformational evolution worked as follows:

> *Oncogenes* initiated lethal cancer in juveniles which created selection pressure in favor of...
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> *Anti-oncogenes* which, because of their inherent pro-replicative nature, increased the germ lines' ability both to avoid the replication imprecisions that caused cancer and their ability to execute development processes in accordance with the genetic program. Their selection decreased cancer rates until such time as changes were introduced by the selection of...
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> *Adaptive pro-oncogenes*. These genes gave the germ lines some survival benefit (more complexity, longer pre-reproductive life, movement to a sunnier habitat, etc.) but increased lethal cancer which was initiated by...
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> *Oncogenes*. More cancer caused selection pressure for more...
>
> *Anti-oncogenes*, which helped the genetic material to produce the new-model animals...

And so on. Through the ages, those three kinds of genes worked collectively as a powerful *engine of transformation*. It was this cycle of

cause-effect-cause, or creation-destruction-creation, that accounted for the great increase in the animal germ lines' ability to produce organisms of wondrous complexity. This powerful transformational *ratchet* explains why vital organs are found only in animals. The *kinds* of organs the animals acquired were, of course, largely determined by *natural* selection, but as plants, jellyfish and sponges demonstrate with great clarity and force, the theory of evolution by natural selection cannot possibly account for the existence of *any* organs of "extreme perfection and complication". Something else must have been involved. Cancer selection is the missing biological entity.