The Biology of EVIL

Part 1: Progenitor and the T-Virus

A series of essays on the science behind Resident Evil

By Hieronymus and The Doctor

For Project Umbrella
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“Real world virology and Resident Evil are not friends.”

—El Bastardo

For a series of games about viruses and medical experiments, Resident Evil is pretty light on actual scientific information. It’s a good thing, too, because whenever Capcom tries to get technical, it becomes obvious that they wouldn’t know real SCIENCE if it bit out their throats.

We know that Resident Evil is just fiction, and that the biological horrors of Umbrella and Tricell exist only to provide a story and a conflict for the protagonists to overcome. It’s equally obvious that a lot of what we see in the games is flat-out impossible. But as men of SCIENCE, we feel it is our duty and our privilege to dig through the evidence—the files, the dialogue, the gameplay itself—to work out how these viruses and monsters would work if they could work at all.

The following report represents our efforts to date; so far, we have only discussed the Progenitor Virus and the T-Virus, but the other viruses are coming. We haven’t begun any work on B.O.W.s or mutant organisms, but that’s also on our agenda. We’ve relied on speculation more than we would like, but we’ve always tried to fit out theories to the evidence, and we’ve relied on real scientific information as much as possible. Handy scientific definitions have been provided at the bottom of each page, and literature citations are available at the end. It should be noted that this report does assume a certain familiarity with the games, but most of the in-game files and assorted game-related information can be accessed through Project Umbrella.

Progenitor

We began our efforts with the one virus from which all others in the series are derived – the Progenitor Virus. Its existence was first hinted at in Code: Veronica, far from an early entry in the series; but since then, Progenitor has come to rival even the T-Virus in the Resident Evil mythos.

Code Veronica (and an EX file in the N64 version of Resident Evil 2) tell us little about the virus itself; only that it was discovered by Spencer, Ashford, and Marcus at some point, and the T-Virus was derived from it.

We learn more in Resident Evil 0. The B.O.W. Report is particularly helpful. The file tells us

This is what Capcom apparently thinks a virus looks like. It’s actually a molecule called uroporphyrin, which is found in small concentrations in urine. Source: Wesker’s Report

The closest we have to an image of purified, concentrated Progenitor Virus is this image of Wesker’s experimental virus. Source: Umbrella Chronicles
that Progenitor has related, but distinct, effects on different animals; lower organisms typically exhibit extreme growth and changes in aggression, while mammals seem to exhibit muscle growth and aggression, but little change in actual size.

In *Resident Evil 5*, everything finally becomes clear. Not only do we find out that Wesker’s powers are due to a variant of Progenitor, we also learn a bit about the early history of the virus. *Resident Evil 5*, more than any other game, is key to understanding Progenitor.

What information we have about Progenitor – and indeed, most viruses in *Resident Evil* – falls into two broad categories: origins and symptoms. Since an understanding of the symptoms can, in this case, better help us to understand the biology of the virus, that’s where we’ll start.

We know from *Resident Evil 0* that Progenitor has different effects based on the species which is infected, and we know from *Resident Evil 5* that the virus also has different effects based on the individual infected. We’ll start by discussing symptoms in humans, and then try to extrapolate what we know to the other organisms.

**Death**

In humans, Progenitor infection can have one of two results. We know from the results of Project W and from File No. 7 on the Ndipaya tribe that most people who are infected with Progenitor, whether by ingesting Sonnentreppe or by direct injection, simply die. (We’re aware that Wesker’s virus was simply called “an experimental virus” in File No. 12 on Albert Wesker; however, we believe it was derived from Progenitor, so we’re going to try to learn what we can from its effects.) We are never told just how these people die, but we can make some guesses.

After working on the Progenitor Virus, we tried to dissect the mechanisms behind the T-Virus and its effects. Our conclusions will be more fully outlined later, but we know that, basically, the difference between the T-Virus and Progenitor is that, while both viruses kill people, the T-Virus keeps the bodies walking. (That’s not *entirely* accurate; we don’t think of T-Virus victims as being actually “dead” in the medical sense, but it will work for now.) Therefore, Progenitor probably kills people the same way the T-Virus does – and we believe the T-Virus kills people through a *superantigen*. This superantigen would cause systemic inflammation and subsequent necrosis of the skin and the outer layers of connective tissue, leading to septicemia and shock, not to mention fluid loss and exposure to all kinds of nasty secondary infections. Our rationale for this mechanism will have to wait until we discuss the T-Virus itself.

We might note that, to our knowledge, this lethal effect applies only to humans. The B.O.W. Report in *Resident Evil 0* indicates no such problems with lethality in animal hosts, suggesting that the hypothesized superantigen is highly species-specific.

Assuming for now that our superantigen hypothesis is correct, we might assume that those individuals like Albert Wesker, who can survive infection, do so by modulating their immune response. If these hosts possess more-effective regulatory T-cells, then they can shut down the sort of immune overreaction caused by a superantigen. This ability would also make them more likely to survive numerous real-world diseases, including the dreaded smallpox. Alternately, it’s possible that high levels of testosterone are down-regulating certain parts of the immune system, preventing over-response to the superantigen; a recent study found that chimps with high testosterone levels generally carry more parasitic infections. High testosterone levels also

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1 Superantigen (SAg): A group of antigens capable of initiating a large, non-specific immune response in a host. This detrimental influx overwhelms the body and can have fatal consequences if left unchecked.
correlate with “alpha-male” behavior, and so would correlate with being king of a civilization of warrior-architects or being a sunglasses-wearing megalomaniac.

We did briefly discuss an alternative theory. It may be that, instead of killing through systemic inflammation and necrosis, Progenitor kills by causing massive inflammation in the brain. Due to stronger expression in the T-Virus, this inflammation would destroy the frontal lobes of most infected individuals – leaving only one in ten million people with a brain intact enough for the subject to be made into a Tyrant, as described in Wesker’s Report II. The necrosis would be a separate issue, caused by the addition of leech genes to the T-Virus – we will explain later how these genes might contribute to necrosis. Ultimately, we dismissed this theory; as we will explain later, the T-Virus can cause zombification more rapidly than a virus could possibly replicate, and our superantigen presents a good explanation for that. Furthermore, many creatures created using the T-Virus, such as Hunters, do not show the kind of necrosis seen in zombies. If we assume the leech genes don’t cause necrosis by themselves, and the superantigen does, the superantigen solves that riddle easily – as we will explain in our next Report.

Strength, speed, and healing

Progenitor is far more interesting when it keeps people alive. We know from multiple encounters with Albert Wesker that whatever virus he was administered gave him super-strength, speed, agility, and healing powers. It’s hard to know if the virus caused these effects because it is based on Progenitor, or because it is an experimental variant of it. However, Chief Researcher Brandon’s Journal No. 1 also suggests the flower “Stairway to the Sun” gives people who ingest it “incredible abilities.” File No. 7 on the Ndipaya tribe indicates some youths consumed the flower in order to fight off Umbrella agents violating their ruins. These files lead us to believe that Wesker owes his powers to Progenitor.

We can only speculate on the source of these abilities, but at the base of everything is metabolism. Wesker needs energy to run faster, punch harder, dodge bullets, and heal from small explosions and steel beams to the face. We think Progenitor up-regulates a number of hormones, particularly thyroid hormones and hypothalamic trophic hormones, and probably a lot of intermediate metabolic enzymes as well. Which ones? We dunno, all of them. To be honest, there are quite a few, and the interactions between them are quite complex. In order to increase growth and basal metabolism without causing serious pathological consequences, they would all probably need to be tweaked somewhat. Fatty acid catabolism to provide energy would keep subjects fit and healthy. Metabolic up-regulation would also help to promote rapid healing. Progenitor may also
aid healing by maintaining populations of stem cells in the body.

However, in humans, a normal part of healing involves the formation of scar tissue. Wesker gets burned pretty badly in the finale to *Code: Veronica X*, but five years later, in *Umbrella Chronicles* (and in *Resident Evil 4* and *5*), he looks just fine. Something needs to account for his lack of disfigurement.

Perhaps Progenitor simply reactivates silent genes from deep biological history; the same genes that allow reptiles to produce functional tissue instead of scar tissue in response to injury. Evolutionary developmental biology and junk DNA\(^2\) suggest many such ancient genes might still be intact (or mostly intact) in our genetic code, despite not having been used in millions of years. Additionally, if some enzyme, perhaps produced by Progenitor itself and not merely up-regulated by it, were to degrade extracellular tissue, this enzyme might reduce the amount of granulation tissue\(^3\) in scars, allowing them to be replaced by healthy tissues.

Progenitor may silence a gene called P21, either through up-regulation of specific repressors, or through short interfering RNA. Organisms in which P21 is inactivated are able to heal from wounds without scarring; their cells can more easily revert to a pluripotent stem-cell state\(^4\).

On to the matter of super-strength. At the end of *Resident Evil 5*, Wesker removed his shirt for the first time in the series (outside of some rather...misguided fanfiction lurking about the internet). We, being men of SCIENCE, noted calmly and dispassionately that Wesker is ripped – but despite his enviable muscle tone, he doesn’t look much bulkier than when he was a member of S.T.A.R.S. So, while it’s easy to say that Progenitor simply increases expression of certain growth factors, we think that Progenitor also codes for a mutant variant of the myosin\(^4\) light-chain protein, one that’s slightly stronger than what normal humans produce. This stronger light-chain myosin would allow for a stronger power stroke during muscular contraction and would probably give Wesker’s muscles greater tensile strength while contracted. This mutant gene may have a slightly stronger promoter\(^5\) than the original, causing it to be expressed preferentially. It may also be that Progenitor expresses the ACTN3 gene, which is correlated with human athletic performance\(^iii\). This gene is inactive in a large portion of the human population, and Progenitor may augment it with an active variant, or double expression of this gene in populations which already possess it.

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\(^2\) **Junk DNA** - Alternatively described as non-coding DNA, the majority of the human genome contains genetic sequences for which no function has yet been elucidated. “Junk” DNA includes repetitive elements as well as the remnants of ancient genes and viruses.

\(^3\) **Granulation tissue** - A fibrous connective tissue comprised of a myriad of different cell types (e.g. inflammatory cells, new blood vessels) which fills a wound during the healing process; eventually, this tissue is replaced by new skin. A pronounced lesion of granulation tissue is colloquially known as proud flesh.

\(^4\) **Myosin** - A class of motor proteins most abundant in the thick filaments of muscle fibers. Alongside actin, it is responsible for the contraction and relaxation of the muscle.

\(^5\) **Promoter** - A specific nucleotide sequence in DNA that binds RNA polymerase and indicates where to begin transcribing a certain gene.
As long as Progenitor is modifying Wesker’s muscle tissue, it might stimulate his body to gradually increase the percentage of **Type IIb**\(^6\) skeletal muscle (that is, fast-twitch muscle), helping him to move faster. This alteration actually occurs in some forms of real-world exercise and physical conditioning, and happens to be responsible for the awesomeness of the late Bruce Lee.

Wesker’s reflexes could further improve if Progenitor increases the number of ion gates in the nodes of Ranvier, which are regularly-spaced, unmyelinated locations on the axons of neurons. The nodes of Ranvier and the ion channels located there are critical in passing along action potentials. An increase in these ion channels might allow membrane depolarization to occur more quickly, thereby helping his nerves to conduct signal faster, but we’re just speculating there.

Finally, it is possible, though admittedly unlikely, that Progenitor expresses a form of cytosolic phosphoenolpyruvate carboxykinase (GTP), or PEPCK-C. Since PEPCK-C increases a variety of metabolic functions, including adipose tissue proliferation, this variant would have to be expressed solely in muscle tissue; the gene may have a promoter sequence similar to that of skeletal muscle actin, or possibly myosin. Chimeric (recombinant) genes like these are easy to build in a laboratory, but a recombination event of particularly low probability would be required to produce one in nature. Progenitor’s function as a retrovirus may assist in this regard by acting as a **transposon**\(^7\) in the host genome. A recombinant gene like the one described has been found to imbue mice with excellent physical endurance and longevity\(^v\).

**Hearing and sight**

The B.O.W. Report suggests that mammals infected with Progenitor develop improved hearing. The Lickers created by the T-Virus are also frequently described as having excellent hearing. This improvement might come about as a result of the same healing factors described above, which may promote the growth of new **hair cells**\(^8\) in the cochlea of the inner ear. Additionally, Progenitor may silence a gene called GJB2 and replace it with a mutant variant, as we discussed with myosin above. GJB2 codes for a protein called Cx26, a growth factor which has been found to affect hearing as well as skin growth and healing\(^v\).

The B.O.W. Report also describes a slight decrease in visual acuity, and it’s also worth noting that in *Resident Evil 5*, Wesker had a hard time dodging rockets in the dark during the battle on the flight deck. The reason for this ocular degeneration is not clear, but originally we had postulated that the large-scale hormonal up-regulation caused by the Progenitor Virus led to an increase in the secretion of aqueous and vitreous humors – the substances that fill one’s eyeballs. Increased secretion of these materials would lead to increased intraocular pressure, which would in turn alter the shape of the lens and retina – leading to blurred vision.

That was one possibility, but we’ve since stumbled upon another. It could be that the Progenitor Virus up-regulates expression of a gene called sonic hedgehog (and yes, it was

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\(^6\)**Type IIb skeletal muscle**- Fast-twitch muscle fibers relying on anaerobic metabolism to create energy in rapid, powerful bursts of speed. As a result of possessing the highest rate of contraction, this muscle tissue type also undergoes fatigue quicker.

\(^7\)**Transposon**- A segment of DNA that is capable of inserting copies of itself into other DNA sites within the same cell.

\(^8\)**Hair cells**- Sensory receptors with hair-like processes located in the cochlea and responsible for converting sound vibrations into electrical signals for the brain via their oscillation patterns.
Telomeres (red) are protective, repeating DNA segments that get shorter with each cell division. When they disappear, the chromosome becomes susceptible to irreversible damage.

Unfortunately, sonic hedgehog also inhibits another gene, PAX6. This gene is also involved in embryological development, and it has particular importance in the development of the eyes. Like hedgehog, it is also expressed in adults; PAX6 has been found to have a role in maintaining populations of progenitor keratocytes in the cornea of the eye, which synthesize corneal proteins necessary for vision. Inhibiting PAX6 would cause many of these cells to become fibroblastic, preventing the synthesis of these necessary proteins and potentially reducing visual acuity.

We really have no idea why the Progenitor Virus seems to give people slitted pupils or why it changes the color of the iris. It could be a result of recombination in reptilian hosts before humans ever stumbled upon Sonnentreppe and the Progenitor Virus…but that’s just a guess for now.

Longevity

We know from File No. 7 that Ndipaya kings, who were basically chosen for kingship based on their ability to survive Progenitor infection, were known for extreme longevity (at least one king lived hundreds of years).

Telomere function is an active area in longevity research, and not coincidentally, it also comes up in Resident Evil. The enzyme telomerase is described in the Lost in Nightmares scenario of Resident Evil 5, in the file Spencer’s Memoirs 4. Our chromosomes have bits on the end called telomeres. These telomeres are degraded a little bit every time our cells divide, and when they’re degraded too much, our cells begin to fail and we get symptoms like liver spots and death. Telomerase is an enzyme which is supposed to repair telomeres, and we have a little of it – just enough to reduce the rate of degradation, but not enough to prevent it altogether. Apparently individuals infected with Progenitor make a lot more telomerase, inhibiting telomere degradation and natural cell aging in that regard.

Our cells have natural mechanisms to fight tumor formation, but obviously, these mechanisms are not perfect. It is likely that Progenitor plays a role in reducing somatic mutation and fighting cancer; it could accomplish this by up-regulating DNA repair mechanisms, suppressing oncogenes, and up-regulating oncolytic processes. Some Progenitor protein products may also have natural antioxidant capabilities. Antioxidants reduce the amount of reactive oxygen species (radicals) in the body; these radicals can damage DNA and cause cell death or tumor formation. By reducing their presence, Progenitor might eliminate one cause of aging.

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9 Oncogene- A gene capable of transforming normal cells into cancer cells under certain conditions, as in mutation or overexpression.
10 Oncolytic- Pertaining to the destruction of tumor cells.
11 Radical- An atom bearing unpaired electrons, inducing it to participate in chemical reactions to fill their valence shell, and making it highly reactive as a result. In the body, oxygen represents the most common radical found.
Based on current research, we also suspect Progenitor causes short-RNA interference\textsuperscript{12} of genes like Daf-2 or Daf-16\textsuperscript{xiii,xiv}. This gene codes for an insulin-like protein which is involved in the mechanisms which make germ-line cells\textsuperscript{13} (the cells which eventually become sperm and eggs) hardier and more resistant to aging than normal cells.

**Aggression**

The B.O.W. Report in *Resident Evil 0* indicates that insects and mammals infected with Progenitor become more aggressive, and amphibians develop a greater appetite (which may be the only way amphibians can actually show aggression, as far as we know). It stands to reason that Albert Wesker and the Ndipaya kings also exhibit greater aggression, although increased aggression might be hard to detect in a megalomaniac and a warrior-king.

This increased aggression may be due to lower levels of monoamine oxidase A\textsuperscript{14}; decreased MAO-A levels have been associated with violent behavior in humans\textsuperscript{xiii,xiv}. For this reason, the gene for MAO-A has been referred to as the “warrior gene”\textsuperscript{xv}. Monoamine oxidase reduces levels of amino acid-based neurotransmitters like serotonin; artificially high levels of serotonin have been shown to turn lobsters into the lobster equivalent of assholes\textsuperscript{xvi}.

**Fertility and sterility**

Over the generations, there would probably be a lot of evolutionary pressure for the Ndipaya to evolve toward a tribe-wide acceptance of the Progenitor Virus. So why haven’t they?

The obvious hypothesis is that, in addition to superpowers, Progenitor also causes infertility, which we like to think of as its own kind of superpower. There is a problem with this hypothesis, however; the B.O.W. Report from *Resident Evil 0* informs us that monkeys infected with the virus actually become more fertile.

But actually, it all makes sense in a weird sort of way. We’ve already suggested that Progenitor boosts the metabolism and causes the host to produce a lot of hormones. These factors, especially the hormones, might result in increased ovulation\textsuperscript{15}.

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\textsuperscript{12} **Short-RNA interference** - A functional process by which short interfering RNA (siRNA) interferes with expression of a particular gene.

\textsuperscript{13} **Germ-line cells** - The progenitors of gamete cells, germ-line cells can reproduce indefinitely before maturing into ova or spermatozoa.

\textsuperscript{14} **Monoamine oxidase A (MAO-A)** - A structurally distinct form of the monoamine oxidase enzyme encoded by the MAOA gene. The enzyme itself catalyzes the oxidative deamination of primary amines to form aldehydes and hydrogen peroxide; typical substrates include neurotransmitters such as serotonin, norepinephrine, epinephrine, and dopamine.

\textsuperscript{15} **Ovulation** - The discharge of a mature ovum from an ovarian follicle into the uterus.
in females—that is, greater fertility. This increased ovulation might also explain why the Licker β in *Resident Evil 5* developed the ability to reproduce after being infected with Progenitor. The increased metabolism, however, also means a higher core body temperature – not a problem for females and their ova, but a big problem for sperm production in males (hence our extremely vulnerable testicles). If most Ndipaya monarchs were male (and the history of civilizations worldwide suggests they would be), they would be childless. It would therefore become necessary to find a successor some other way – and a tendency to eat poisonous plants is the mark of a good leader.

There is another possible explanation which derives from the superantigen hypothesis presented above. People with relatively weak cell-mediated immunity would be more likely to survive a Progenitor infection, as the virus’s superantigen would have a hard time driving their immune systems into a self-destructive cytokine storm. However, cell-mediated immunity and humoral immunity (the part of the immune system involving antibodies) are often inversely correlated. It turns out that sheep with a strong humoral immunity live longer but are less fertile, as their immune systems attack their own sperm or ova. Likewise, a “genetically superior” Ndipaya king with a strong humoral immunity would be resistant to many common infections and would survive Progenitor infection due to weak cellular immunity, but might have trouble siring a child even without the added effects of the Progenitor virus.

**Unusual animal growth**

The good news is that everything we’ve discussed regarding Progenitor in Wesker and the Ndipaya (except perhaps the fatality rate) also applies when we discuss other mammals, at least according to the B.O.W. Report in *Resident Evil 0*. The bad news is that the effects are totally different in insects.

We’ve suggested before that Progenitor causes increased hormonal expression in hosts. In arthropods, one of the hormones affected could be something called *prothoracicotropic hormone*[^16]. The more of this hormone an arthropod produces, the more often it molts. The more the organism molts, the larger it can grow. So, that’s probably a good place to start. We have also claimed that the Progenitor virus stimulates production of other growth hormones as well.

We see several mutant arthropods in *Resident Evil 0*: the Stinger, the Centurion, and the Plague Crawlers. Unfortunately, none of these are products of the Progenitor Virus – the *Resident Evil Archives* indicate that all were produced by exposure to the T-Virus. Therefore, we don’t know how large insects get when infected with the Progenitor Virus. We do see some insects grow to unusual but believable sizes as a result of T-Virus infection, such as the wasps in *Resident Evil* and its remake, and the cockroaches in *Resident Evil 2*. Given the well-known limits on the size of real insects, that’s probably a good benchmark for insects infected with the Progenitor Virus.

According to the *Resident Evil Archives*, Lurkers are actually products of the T-Virus, not the Progenitor Virus, as the B.O.W. Report in *Resident Evil 0* would suggest. Their extreme growth will be discussed in the essay on the T-Virus.

There are some animals we never see directly, but which appear on some carvings in the Ndipaya ruins. We can assume that they are products of the Progenitor Virus; however, they seem to have been affected to a far greater degree than most other Progenitor subjects. Their digitigrade legs suggest they were never human, but the spikes on their backs do not suggest any normal animal of that size which has lived in the past few million years.

[^16]: *Prothoracicotropic hormone (PTTH)* - An insect hormone that effects release of molting hormone from prothoracic glands thus stimulating the molting process.
We have speculated that these creatures might be beasts of war, created by the Ndipaya by feeding the Progenitor-infected flower Sonnentreppe to some large mammals. That alone would not create the mutations we see, but a breeding program would lead to strange and interesting genetic recombination events as parts of the Progenitor Virus’s genome are randomly shuffled in the process of meiosis and then combined in a new organism. Superinfection might be another factor; superinfection would involve the same cells being infected more than once, as very large quantities of virus are introduced to the animal, perhaps by force-feeding it lots of Sonnentreppe.

Judging by the carvings, this did not go well for the Ndipaya.

**Evolution**

Progenitor is one of the rare viruses which can infect both plants and animals – and more importantly, it’s one of the few which can infect both plants and humans. Some viruses do have limited pathogenicity in humans; a recent paper revealed that the pepper mild mottle virus can cause an immune response, but its effect seems limited to the gut. The cowpea mosaic virus can enter human cells, but cannot replicate within them. The sort of host range necessary for a plant virus to invade human DNA on a systemic level doesn’t just happen; it has to evolve through prolonged contact, and repeated reciprocal infection, between the two hosts. We have absolutely no evidence for the following scenario, but it seems plausible to us:

Thousands of years ago, the Ndipaya tribe moved into a cave system near the west African coast. Deep within the cave, they found a very unusual chamber, where the sun shone in from a hole in the roof and flowers grew deep underground. They called this special place “the Stairway to the Sun,” as described in File No. 7 on the Ndipaya tribe. Equating the sun with the afterlife, they buried their dead tribal chiefs there. As part of a sort of ancestor-worship, they also consumed the flowers which grew over the graves of their tribal chiefs. At this point, consumption of Sonnentreppe cannot have been fatal, or they would have immediately stopped eating it and would never have eventually learned about its beneficial effects in a small group of people.

The flowers, which would someday be known as Sonnentreppe, were infected with a plant retrovirus – one of the few which still exist in nature. As the Ndipaya ate it, perhaps in religious rites, the virus adapted to infect human cells. There is precedent for such rites directly influencing the evolution of other species. Some of

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17 **Meiosis** – The process of cell division by which sperm and eggs are formed.
These particles are human endogenous retroviruses. Our DNA codes for them, but they normally don’t get produced. Some scientists induced these to develop. Source: Löwer et al 1995

these humans were then buried in the Sun Garden, and the virus filtered back to the plants through the root systems. Over thousands of years, this cycle was repeated over and over again.

At some point, the plant retrovirus may have incorporated genetic material from the human hosts who ingested Sonnentreppe. This sort of thing actually does happen with real viruses, and may even be an important evolutionary mechanism. The genetic material taken up by the plant retrovirus could include genes coding for certain metabolic regulators, enzymes, and growth factors. The virus also recombined with an endogenous retrovirus buried in the human genome and long dormant. Such endogenous retroviruses, or ERVs, are common in the genetic code of almost every living thing. These viruses infect organisms and combine their genomes with that of their host, and their genetic code gets passed down just like any other set of genes. For reasons we will get into later, we believe this retrovirus was humanspecific, like the smallpox virus and a few others; furthermore, it contained a superantigen with a very strict binding affinity for human immunoreceptors. This superantigen would be the cause of the virus’s new lethality.

This new, recombinant virus was fed back into the Sonnentreppe population by the burial of the dead. At about this point, people who ate Sonnentreppe started dying. As the victims of Progenitor piled up in the Sun Garden, the virus propagated rapidly, driving the original strain to extinction. But not everyone died – due to a natural immunity, perhaps a mutation in the superantigen receptor, some individuals gained vitality which harkened back to the heroes of old. Naturally, these people tended to become tribal leaders due to their bravery and valor on the field of battle, or in the hunt, or whatever. However, they were unable to bear offspring, and had to choose successors from the population. Over years, the flower-eating practice morphed from a form of ancestor worship to a test of mettle and a means of choosing the next Ndipaya king. The Ndipaya, led by probably the closest thing humanity has ever seen to god-kings, forged a formidable empire centered around their cave-city, with the Sun Garden in the heart of it all. The glorified god-kings were thereafter interred in a space behind the Monarch Room, where their sarcophagi can be found during the first battle with Wesker in Resident Evil 5.

Thousands of years later, a man named Henry Travis would come among the Ndipaya, recording their rituals, myths, and legends. Hundreds of years from then, a man named Ozwell Spencer would read of the tribe and their sacred flower, and start getting ideas – and delusions of grandeur.

Sonnentreppe and viral replication

We’ve discussed the effects of Progenitor in animals. We want to discuss how it reproduces in plants. This is kind of a mystery, since Brandon Bailey’s Journal No. 1 in Resident Evil 5 tells us Progenitor simply couldn’t be found in plants grown outside of the Sun Garden in the Ndipaya ruins.

Bailey’s failure to isolate Progenitor may result from a basic characteristic of latent viral infections: the viral genome may be in the host’s cells, but the virus is quiescent – that is, no new virus is being produced. HIV is known for this kind of sneakiness. It looks like Bailey suspected this, because he and his team tried to grow Sonnentreppe in different soils and light exposures, and he tried variations of every condition he could think of in an attempt to get the virus to express.

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18 Latent viral infection- A stage in the replication cycle of certain viruses wherein production of new virions has halted; since the viral genome is a lingering part of the host, however, the virus can reactivate at any given time, usually in response to environmental factors.
Every Sonnentreppe plant is presumably infected already, and indeed, the infection may be transmitted in the seeds or pollen to each new generation of plant. However, the virus remains latent in the plant’s own DNA unless certain conditions are met. The exact conditions required for Progenitor expression in Sonnentreppe are unknown, but may result from a single gene, such as a transcriptional element, expressed under the conditions of the Sun Garden and nowhere else.

The situation may be quite different when Progenitor infects humans. This virus is obviously able to replicate in plants; however, human tissue may be susceptible to infection but not permissive of replication – that is to say, the virus can get into a human cell and change its DNA, but can’t make new viruses in a human cell to go off and infect anything else.

We base this hypothesis on a couple of factors. First, if Progenitor could replicate in human tissues, Umbrella wouldn’t have needed the laboratory by the Sun Garden after they obtained the virus for the first time. They could get as much Progenitor as they wanted just by growing their virus in human subjects and sucking out the precious, virus-laden fluids. Instead, they expanded the laboratory and kept it running in secret for decades.

The properties of the G-Virus also suggest that it may not be able to replicate in human cells – in order to create a new G-Type, it has to transfer embryonic tissue into a new host rather than merely transmitting infectious fluid like blood or saliva. We wondered why the G-Virus might be engineered to be replication-incompetent, and the simplest answer was that it wasn’t engineered that way – the trait was a holdover from the Progenitor Virus from which it was derived. (We’ll go into more detail about this in the third Report.)

The kind of effects produced by Progenitor infection in humans require a major shift in the body’s homeostasis. Such an effect could be produced by infection of every cell in the body, although if the virus is incapable of replication this would require an extraordinarily large inoculum (something we’ve calculated to be just about barely within the realm of possibility, given the volume of material we see Wesker inject himself with). Another possibility holds that only a small proportion of the body’s cells are infected, but the hormones and growth factors produced by these cells are enough to alter the body’s homeostasis. This ties in to a possible explanation for Wesker’s plot serum in Resident Evil 5, which we will describe later.

Retrovirus

We’ve talked rather a lot about what Progenitor does; now we’d like to discuss what Progenitor is. Our hosts at Project Umbrella have an informative page on Progenitor which describes it as a retrovirus. Retroviruses are unique for two reasons: first, they are able to “reverse-transcribe” their genetic material, which they store as RNA, into DNA inside of a host cell. Second, they can integrate this DNA into the DNA of a host cell, becoming a permanent part of that cell, instead of leaving their genetic material floating around in the cytoplasm.
These characteristics, particularly integration, make the retrovirus classification a very good candidate for the group to which Progenitor belongs. Numerous files throughout the *Resident Evil* series also seem to support the theory: Wesker’s Report II describes the “Founder Virus” (Progenitor) as an RNA virus able to modify genes; the *Resident Evil 5* file Brandon’s Journal No. 1 claims James Marcus hypothesized a virus which could alter DNA; File No. 1, History of *Resident Evil*, claims Progenitor can “reconstitute” a living organism’s DNA.

Wesker’s Report II also astutely notes that RNA viruses are prone to mutation, which could explain a lot of the physiological transformations we see in organisms like G-Types and Umbrella’s “ultimate weapon,” T-ALOS. Retroviruses, it turns out, are especially prone to mutation due to the low fidelity of the reverse transcriptase complex.

We have come to the conclusion that Progenitor is indeed a retrovirus, for those reasons and more. At first, however, we were not convinced. All viruses are able to insert their genetic material in a host cell, essentially altering that cell’s genetic content, even if the cell’s chromosomal content is not altered by integration. It may have been possible for another virus to insert genetic material which might cause unusual effects, without this material ever entering the nucleus and becoming part of the subject’s genetic code. Furthermore, we have learned that there are no currently known plant retroviruses.

We investigated a number of viruses, including rhabdoviruses and toposviruses, both of which can infect both plants and insects. Rhabdoviruses include the rabies virus, which has obvious similarities to the behavioral effects of the T-Virus. Ultimately, however, we returned to retroviruses. While there are no plant retroviruses currently known to exist, there is some evidence in the form of retrotransposons and other retroelements which point to such retroviruses existing in plants in fairly recent biological history. More importantly, the B.O.W. Report in *Resident Evil 0* describes effects of the Progenitor Virus being passed from one generation to another. These traits could only be inherited if the virus integrated its genetic material into the host genome, as a retrovirus would.

Wesker doesn’t look like he is experiencing a lot of tissue damage as a result of Progenitor infection. Therefore, Progenitor probably replicates by exocytosis. In exocytosis, mature virus particles are enveloped

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**Reverse transcriptase (RT)**- Also referred to as an RNA-dependent DNA polymerase, this enzyme transcribes RNA into DNA thus preparing the viral genome for integration into the host’s DNA. Unlike conventional DNA polymerases, however, reverse transcriptase lacks a proofreading mechanism during transcription; this leads to an accumulation of genomic errors, hence why RNA viruses using RT tend to mutate so rapidly.
in vesicles which merge with the cell membrane, expelling the virus into the intercellular space without damaging the cell membrane. This mechanism leaves host cells alive, rather than destroying them as in the classic lytic cycle\textsuperscript{21}. Another form of exocytosis, budding, would involve the virus taking a piece of the cell’s membrane with it, giving Progenitor a viral envelope\textsuperscript{22}. Budding is common in retroviruses which produce latent infections. However, if the virus replicates too rapidly, budding can deplete the cell membrane, killing the host cell.

**Infection**

Progenitor can infect species ranging from plants to insects to humans. Infection of plants is not a problem, since the virus typically enters the cytoplasm of the plant’s cells directly. However, in order to infect animal cells, the virus must first attach to receptor proteins\textsuperscript{23} on the cell’s surface. In order to create the drastic changes we see in most Progenitor hosts, the virus would have to infect nearly every cell in the host’s body.

These facts give us three requirements for the host cell receptor to which Progenitor must attach: It must be located on the cell surface; it must be present in nearly every animal species; and it must be present in nearly every cell in the body. We therefore believe Progenitor responds to a phospholipid, perhaps phosphatidylserine.

Every cell in nature has a plasma membrane, also known as a cell membrane – a thin skin of phospholipids that separates the goo inside from everything outside. There are a number of types of these phospholipids – phosphatidylcholine is one of the most common types – but, compared to the nigh-infinite array of surface proteins produced by different cells and organisms, the number of phospholipid types is relatively manageable. Every cell in the human body – and every cell in everything else, ever – uses more or less the same phospholipids, albeit in different proportions. That means that a virus which targets phospholipids could infect an enormous variety of animals, and could infect every tissue in a given animal – two very important characteristics of Progenitor and the T-Virus.

There is a real-world virus, the vesicular stomatitis virus, which has a similarly wide range of cells that it can infect (it cannot replicate in all of these cell types, but we’re not worrying about that). For a while, scientists believed that vesicular stomatitis virus bound to phosphatidylserine on host cells – while we now know that the whole story is a little more complicated, it appears that phosphatidylserine may still play an important role.\textsuperscript{xxv,xxvi} It’s within the realm of possibility that Progenitor and the T-Virus could achieve cell entry in a similar way.

**The Trevor Family**

A few things remain to be discussed – namely, the variants and derivatives of the Progenitor Virus.

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\textsuperscript{20} **Exocytosis**- Also referred to as budding, this process involves the non-destructive discharge of virions from a cell, effectively reducing it to a continuous viral factory. Many enveloped viruses causing persistent host infection (e.g. HIV, HSV-1) preferentially exit in this fashion. Exocytosis can also involve vesicular transport outside the cell, preserving the cell membrane.

\textsuperscript{21} **Lytic cycle**- The most well-known method of viral egress whereby progeny virions burst en masse and destroy the host cell.

\textsuperscript{22} **Viral envelope**- a lipid membrane coating a virus, typically aiding attachment and penetration of host cells.

\textsuperscript{23} **Receptor proteins**- A molecular structure present upon a cell’s plasma membrane to which a virus must attach in order to be integrated into the cytoplasm.
In the remake of *Resident Evil*, one file, the Family Picture and Notes, describes two early Progenitor experiments in which the women of the Trevor family are administered two experimental variants – Type A and Type B. The file goes on to describe – using the real, but completely non-applicable term “plasmolyzing”\(^\text{24}\) – how only Progenitor Type B results in “viral fusion” (though it should be noted that in the original Japanese text, the file refers to “tissue fragmentation” rather than “plasmolysis”). If Progenitor has a viral envelope, it would indeed be capable of viral fusion, in which its envelope merges with the cell membrane, inserting the naked virus into the cell; more importantly, as a retrovirus, it would be capable of genetic fusion, and in fact this trait is one of the reasons it was so important to Ozwell Spencer. But why would only one of the two variants be capable of fusion, and why didn’t it kill Lisa Trevor?

The first possibility is the simplest, but relies on chance to the extent that it feels like a cop-out. It may simply be that Lisa Trevor possessed the genetic qualities necessary to survive Progenitor infection, and her mother Jessica did not. It is entirely possible for Lisa to have this trait, even if her mother and father do not. Thanks to the intricacies of inheritance, some traits, such as eye color, rely not just on a single gene, but on an interplay between several. The trait allowing some individuals to survive Progenitor infection may be an example of this kind of inheritance. However, this explanation ignores the fact that two different versions of Progenitor were being described.

We might also speculate that, in researching Progenitor, Umbrella decided the high fatality rate in humans was an intolerable stumbling block. Ozwell Spencer would later rely on Progenitor’s propensity for genetic selection in Project W, but the virus would do him no good if it presented a very high probability of killing him. Umbrella’s researchers may have modified Progenitor in an attempt to remove the lethal factor – a difficult prospect if the superantigen happened to be necessary for infection, replication, or exocytosis. Lucky Lisa Trevor received a functional, nonlethal version. Her mother either received a nonlethal, non-functional version (the most likely hypothesis if the virus could not fuse with her cells), or a fully functional, fully lethal version (which would prevent viral fusion by killing the host before fusion could take place). Some may feel that the Family Picture and Notes implies that Lisa Trevor’s Progenitor Type B went on to become the basis of the T-Virus; however, based on our understanding of the lethal factors of both the T-Virus and Progenitor, we would suggest that Progenitor Type B was never further developed. Spencer may have intended to use this strain as the base for his immortality virus, as described in Spencer’s Memoirs 1 and 2, in the Lost in Nightmares scenario of *Resident Evil 5*.

**The Wesker Virus**

We have assumed throughout this essay that the virus with which Albert Wesker injected himself is the same as, or is very similar to, the Progenitor Virus. We make this assumption because Progenitor is known from several files to cause physiological changes in humans, and these changes are hinted to physically improve those who survive infection. We also know that Spencer saw the Progenitor Virus as the key to Project W (or the Wesker Virus).

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\(^{24}\) **Plasmolysis**- the process in which the plasma membrane of a plant cell detaches from the cell wall due to reduced cytoplasmic volume.
Plan; *Resident Evil 5* isn’t really consistent on a title). So while File No. 12 on Albert Wesker calls the virus “experimental,” we’re pretty sure it’s still quite similar to Progenitor.

However, the virus is also described in *Umbrella Chronicles*. In the Virus Memo, William Birkin claims that the virus is “designed to conquer death.” When animals are injected with the virus prior to severe injury, they supposedly have a 90% rate of full recovery, and a 70% chance of improved cardiovascular and muscular performance. These statistics contradict not only what we know about the Progenitor Virus (which kills most individuals who are infected), but also what we know about the virus given to the Wesker Children (most of whom died).

We came up with several theories to try to explain this discrepancy. The simplest theory is that William Birkin was simply lying about those statistics. Under this theory, Ozwell Spencer gave Birkin the virus and ordered him to get Albert Wesker to take it. Birkin, fearing Spencer would cancel his G-Virus project, betrayed Wesker and provided him with the virus under the pretense that it would allow him to fake his death. It was only sheer luck that Wesker had a genetic code which would allow him to survive Progenitor infection and so the virus worked as advertised.

It’s a plausible theory, but as men of SCIENCE, we don’t like to throw away statistics and physiological data that are dangled in front of us like so much red meat. We started looking for other ways to integrate the Virus Memo into our knowledge of Progenitor.

In our second scenario, William Birkin is actually describing a second virus of his own design – a **helper-dependent virus** lacking the genetic hardware to replicate by itself, which Birkin provided along with the virus Spencer gave to him. This virus would contain genetic modifications necessary to allow Wesker to survive infection by the experimental virus, and would use the experimental virus to replicate itself. The problem with this theory is that it introduces a wholly new virus which has never been mentioned in any of the games.

Our third scenario simplifies our second. We supposed that, after Spencer gave Birkin a sample of the experimental virus, Birkin went to work on it himself. Being the genius that he was, he modified the virus, removing the lethal characteristics and perhaps adding a few new features which would increase Wesker’s odds of survival. What a loyal friend…

Unfortunately, we decided that Birkin probably would not have gotten away with that. That kind of work could take days or weeks (or months or years in real life), and we know that Umbrella has an internal spy network. This network, Monitor, would probably have noticed Birkin modifying Spencer’s virus.

We consider this next and final scenario to be the most plausible. Ozwell Spencer provided William Birkin with a sample of Progenitor Virus “from the mutation stocks,” but did not tell Birkin anything about it. Birkin ran some tests, injected small amounts of the virus into rats, and found that most of them survived and showed extreme physical improvement. This kind of work could be done over a long weekend, or perhaps an evening, and could be done by a single person, perhaps allowing Birkin to avoid the scrutiny of Monitor. Birkin would have relayed these statistics to Wesker and gave him a sample of the virus.

Birkin noted that the virus was not tested in humans. What he didn’t know is that this experimental virus, like the Progenitor Virus itself, may be harmless to rats, but the viruses are usually lethal to humans, due to the

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**Helper-dependent virus** - A virus incapable of completing its replication without the presence of a helper virus, which contains the enzymes that the helper-dependent virus does not possess in its own genome. Dependoviruses are an example of this type of virus.
specificity of the superantigen lethality factor. Hence, everything in the Virus Memo is technically correct, but its information is incomplete.

It is important to note that Birkin specifies that the virus has the greatest effect when the subject is infected about five minutes prior to severe physical trauma. This could indicate that hormones released as a result of stress and injury dramatically up-regulate the expression of Progenitor genes, or at least help to kick-start the body into expressing them for the first time. Progenitor may therefore share a promoter with certain vertebrate stress-activated genes such as those in the SAPK pathwayxxvii. This doesn’t come up much in the games with regard to Progenitor, but we will see it again when we describe the T-Virus.

One more note about the Wesker Virus. In the file Wesker’s Notes on Differing Mutations in Umbrella Chronicles, Wesker considers the way Sergei Vladimir mutated after injecting himself with “the virus” and speculates that the effects of this virus may be tied to the host’s state of mind. We have no way of knowing what virus Sergei infected himself with (although we have some theories which we will get to in a later installment), but Wesker wonders what implications there might be for himself if the virus actually does reflect the host’s mental state.

There are cases in which a host’s mental state can affect certain physiological conditions such as inflammation or the general state of one’s health. The placebo effect is a great example; recent studies have suggested these effects may be as much biological as psychologicalxxviii. However, Wesker himself admits he has no evidence for his theory, and given the enormous difference between his mutation and Sergei’s, we think his theory is a bit daft. Wesker bases his claim on intuition, but his intuition didn’t save him from getting dumped into a volcano. So there.

P30

Resident Evil 5 introduces us to two derivatives of the Progenitor Virus: P30 and PG67A/W.

P30 is an “ancillary chemical” discovered by Wesker during his research on the Progenitor Virus; he used the substance to control Jill Valentine. It has two effects: it imbues the subject with almost superhuman speed, strength, and agility; and it renders the subject highly susceptible to suggestion. The only drawback is that the host’s body rapidly metabolizes the chemical, so its effects last only a short time unless it is administered continuously.

That first collection of traits – the speed, strength, and agility – will sound awfully familiar after the above discussion of the effects of the Progenitor Virus. We suspect P30 is a modified version of a chemical or protein synthesized by the Progenitor Virus in a host. This chemical may be one of several master substances which alter the hormonal balance in the host, increasing metabolism. Like some known trophic hormones, this substance could affect the production of a wide variety of other hormones, up-regulating some and down-regulating others.
However, Progenitor is known to cause aggression, while P30 blots out free will. We are not neurochemists, but it’s possible that aggression, reason, and decision-making depend on similar chemical signals. We submit that the master chemical from which P30 is derived may also be the trigger for increased aggression in Progenitor hosts. If P30 were modified to increase aggression, these modifications might have unintended consequences, and may actually reduce an individual’s ability to use reason or to make decisions for himself or herself.

P30’s remarkably short half-life may be due to the action of a plasma-borne peptidase, suggesting P30 has a natural human analogue to which such a peptidase might be specific.

PG67A/W

In Resident Evil 5, Albert Wesker had to periodically inject himself with a serum designated PG67A/W. Jill Valentine explained that the serum helped to keep the virus in Wesker’s body in a delicate balance. Too little serum and Wesker might lose his powers; too much, and the serum could act as a poison.

The syringes containing the serum (and their cases) were printed with the Tricell logo and what looked like a label from a template. The serum is probably produced at a Tricell facility, more than likely either the Uroboros research facility in Africa, or the smaller facility on the freighter. We cannot state with certainty that it was initially developed by Tricell, rather than brought to them by Wesker, but that seems pretty likely to us.

No evidence was ever provided before that Wesker needed regular inoculations of anything to help him maintain his powers. For that matter, there is no evidence that B.O.W.s or other creatures infected with Progenitor-derivative viruses need regular injections. Some individuals on the Project Umbrella forums have speculated that Wesker only recently developed the need for booster shots. If Wesker needs this shot, it is probably due either to the experimental nature of the virus in his body, or to PG67A/W augmenting his powers rather than being completely responsible for them.

What does PG67A/W mean? It may be that PG67 is the real name of the Wesker Virus, although we have no proof for this assertion. Making that assumption, we’re pretty sure PG stands for Progenitor; 67 stands for either the year the Wesker Virus was created or the start of Project W; and W stands for Wesker. The A could stand for anything, depending on what the serum actually does. We’ve gone through a number of different theories regarding its function.

1. PG67A/W is the Wesker Virus, or even Progenitor itself. It’s possible that Wesker might simply be taking “booster shots” of the virus that gave him his powers. An overdose might lead to superinfection, which could have unpredictable results including tissue damage and death.

This theory is supported by the fact that Excella Gionne was seen with two attaché cases full of the serum in a small laboratory containing the Progenitor-infected Sonnentreppe flowers – she was using the flowers to produce PG67A/W. It’s even possible that these flowers were infected with the Wesker Virus rather than Progenitor.
Unlike many viruses, retroviruses remain in the host for life. If Progenitor is a retrovirus, and if it is able to reproduce in human cells, then there should be no need for Wesker to reinfect himself on a regular basis. If, on the other hand, Progenitor is unable to reproduce in human cells, then we might presume that only a small proportion of Wesker’s cells are infected at any one time. As we discussed above, these cells may still be able to alter the levels of hormones and growth factors in Wesker’s body in such a way as to explain his powers; however, the higher metabolic activity of these cells may or may not lead to an increased rate of cell death. The gradual depletion of these infected cells from Wesker’s body would require that Wesker continually reinfect himself to maintain his powers.

It should be noted that if this scenario is the case, then any presumed DNA damage-repair mechanisms, including increased telomerase expression, would either become irrelevant or would have to be triggered in uninfected cells through as-yet unknown signaling mechanisms.

2. PG67A/W is a castrated form of Progenitor. Retroviruses express a protein called integrase, which allows them to paste their genomes into a host cell’s DNA. This variant of Progenitor might have had its integrase gene modified or deleted in order to prevent the kind of unwanted mutation that can crop up when you stick foreign genes into your DNA. However, knocking out integrase also means that the virus cannot replicate itself and that any new genetic material it brings to a cell will eventually be degraded. As a result, Wesker would need regular injections to maintain the effect.

If Wesker’s secret sauce is indeed a mutated form of Progenitor, it could have been created for one of two reasons. It may be something Wesker developed himself to increase his powers by over-expressing Progenitor genes; this would explain why he appears to have taken a level in badass since the events of Code: Veronica. Alternately, this strain may be the Wesker Virus itself—it is possible that Ozwell Spencer was wise enough to realize that one of his Wesker Children might betray him, so he made sure that any powers they gained from infection with his experimental virus would not be permanent. Unfortunately for him, it didn’t stop Wesker from making more of the stuff.

3. Our current favorite theory holds that PG67A/W may be a substance which increases Wesker’s powers, perhaps by increasing transcription of viral proteins. Some phenotypes induced by Progenitor infection, such as super-strength, speed, and agility, may fade over time as the host’s cells shut down the expression of foreign proteins—this may be what Jill meant when she said the virus was unstable. This shutdown happens occasionally in genetic engineering. Not a problem for an Ndipaya king (clearly, though, the longevity genes continue to express); but Wesker likes being able to dodge bullets and punch through the ribcage of an invalid. Hence, he designed this activator[^26]. An overdose might cause an acute hormonal imbalance which might severely impede his ability to fight or even to stay conscious.

Additionally, in Resident Evil 5, Wesker moves so rapidly he appears to teleport. He has never moved so quickly before, even after he was infected with the virus (and he’s had plenty of opportunities). If PG67A/W is an activator, it may responsible for Wesker’s upgraded powers. Without it, his powers may decrease to what

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[^26]: Activator - A protein which binds to DNA and stimulates transcription of a specific gene.
was shown in *Code: Veronica* and *Umbrella Chronicles* – impressive, but short of the Agent Smith-inspired moves of *Resident Evil 5*.

According to this scenario, A/W may mean “Activator/Wesker.”

**T-Virus**

Progenitor may be the mother of all *Resident Evil* viruses, but in terms of lives lost, B.O.W. research conducted, and overall presence in the games, the Tyrant Virus reigns supreme.

We are first introduced to the T-Virus in the original *Resident Evil*, where we learn that it makes zombies and monsters. As interesting as that is, we don’t learn much else until much later, when Wesker’s Report II and *Resident Evil 0* are released. There, we finally learn a little more about the origins of the T-Virus – which we will discuss later.

The T-Virus seems to have three categories of effects: most humans and other mammals which are infected become zombies; most other organisms mutate unpredictably into things big and scary; and when used under controlled, laboratory settings, the T-Virus can apparently be used to design monsters. So far, we have tried to understand the first two effects of the virus, and we have some ideas about the third; those ideas will have to wait for the next installment of this Report.

*Resident Evil 0* explains that the T-Virus was created as a result of James Marcus splicing leech DNA into the Progenitor Virus. Where possible, we will try to explain what traits we think are a result of Progenitor, and what traits were introduced with the leech DNA.

We will discuss T-Veronica later, in its own essay. The NE-T Virus will be dealt with when we get to Nemesis and other B.O.W.s.

**Necrosis**

The first thing someone will notice about a person infected with the T-Virus—before the moaning, the shambling, the hunger for human flesh—is the decay. T-Virus zombies look like they are rotting. This decomposition could come about in one of several ways.

The simplest explanation is that the virus replicates uncontrollably, lysing host cells and destroying tissues. This explanation is fairly solid, and should not be overlooked, but T-Virus infection can cause decomposition and brain damage in minutes rather than the hours a normal virus would need at minimum.
We would like to see an explanation that works more rapidly. Furthermore, we assumed earlier that Progenitor does not reproduce by lysis, so in theory, neither should the T-Virus.

A second explanation involves the superantigen we’ve been invoking throughout the Progenitor section. In fact, rapid zombification is the reason we introduced the superantigen theory in the first place.

A superantigen is a protein built to kick the host’s immune system into overdrive. While it might seem counterintuitive for a virus to actively overstimulate the host’s immune system, this phenomenon is common, and such overstimulation actually helps the virus evade immune detection.

When stimulated by a normal antigen, a form of white blood cells called cytotoxic T-cells (which have nothing to do with the T-Virus) produce cytokines, perforins, and other substances designed to kill target cells, like those infected with a virus. When the immune system is overstimulated, a cytokine storm can result. In a cytokine storm, so much of these cytotoxic chemicals are released that the body’s tissues begin to die – a condition called necrosis. It is only a matter of time before this dead tissue begins to rot, and it can look nasty enough long before that.

There is no plausible way that leech DNA could be involved in either of these mechanisms. We suspect that this superantigen must have come from Progenitor.

A third explanation, to which we alluded at the beginning of this Report, holds that the body of an infected individual begins to actively consume its own proteins as a source of energy. We believe that the leech DNA which was incorporated into Progenitor to create T may contribute certain metabolic enzymes and hormones which would accelerate this process; we will elaborate further on this topic shortly. Degradation of host proteins helps to explain a zombie’s rotted appearance, but it fails to explain the extremely rapid onset of behavioral changes – changes we believe are better explained by the superantigen hypothesis.

We believe that necrosis and decomposition is (mostly) limited to the skin. Obviously, zombies need most of the brain (but obviously not all of it), nervous system, and muscles intact to move and seek prey. We do have some theories as to how these tissues survive when everything around them is dead, and we will get to those theories shortly. We also know that zombies can remain active for several months (the T-Virus spread through the Arklay Mansion on May 11, 1998, and zombies were still shambling through its halls on July 24). Finally, we know that, depending on the stimulus and T-Virus strain zombies become either Crimson Heads or Lickers, and both appear very metabolically active, despite the ruptured capillaries and loss of skin.

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27 Cytokines- A generic term referring to signaling proteins released by immune cells in generating a response to a pathogen. Cytokines therefore control the strength and duration of an immune response thus they serve as immunomodulators in this capacity.

28 Perforins- A cell-destroying protein which acts by forming pores in the plasma membrane of a cell, facilitating its eventual lysis.

29 Capillaries- The body’s smallest blood vessels which not only connect arterioles and venules but also serve as semipermeable membranes for the interchange of various substances between blood and tissues.
We therefore believe that many vital organs (such as the heart, lungs, pancreas, and assorted glands) and major blood vessels in the body’s core must remain alive, even if they are damaged by septic shock\textsuperscript{30} and function at lower levels than before. They are probably reactivated in full during the Crimson Head transformation (for reasons we’ll get to later). In this light, we suspect that the T-Virus (and probably Progenitor) preferentially targets the skin and tissues of the outer integument\textsuperscript{31} for replication. Any superantigen produced probably remains largely concentrated in those tissues. Some virus, of course, must make its way into the core tissues in order to cause the transformations which will be discussed later.

**The Living Dead**

We have already explained why the T-Virus causes rotting, and we’ve speculated that Progenitor uses the same mechanism to kill people. This rotting would shut down blood circulation, cutting off the supply of oxygen and nutrients to important tissues like the brain. Why, then, don’t T-Virus victims stay dead?

This is where the leech DNA starts to come in. Metabolism in animals can be said to occur in three stages: glycolysis\textsuperscript{32}, the Krebs cycle\textsuperscript{33}, and the electron transport chain\textsuperscript{34}. The electron transport chain, and the ATP synthases\textsuperscript{35} which are driven by it, produce the most usable energy by far of any of the three stages. The electron transport chain is also the only stage in the process which requires oxygen. Glycolysis and the Krebs cycle are both anaerobic\textsuperscript{36} processes; human cells cannot survive on these processes alone, but both do provide some usable energy. Glycolysis causes increased acidity which is usually counteracted by the electron transport chain.

Animals have another anaerobic metabolic pathway – fermentation. Fermentation allows muscles to keep functioning even when oxygen reserves have been exhausted, generating lactate as a byproduct.

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\textsuperscript{30} Septic shock- An occurrence induced by severe infection where the body’s vascular system is overwhelmed as a result of the pathogen’s specific virulent factors, such as an endotoxin or superantigen. The systemic nature of this condition taxes the body to fatal levels.

\textsuperscript{31} Integument- The organ system covering the body which consists of the skin, including its various layers, and its associated appendages.

\textsuperscript{32} Glycolysis- The splitting of glucose into pyruvate through a series of ten reactions. This metabolic pathway is known to occur in all living cells, underscoring its universal importance in the biochemical reactions of both aerobic and anaerobic organisms.

\textsuperscript{33} Krebs cycle- More commonly known as the Citric acid cycle, this eight-step metabolic pathway completes the conversion of glucose into carbon dioxide. This effectively transforms molecules of carbohydrates, proteins, and fats from foods into energy usable by the cell.

\textsuperscript{34} Electron transport chain- A linked set of enzymes that perform mediating biochemical reactions which, when coupled with the process of oxidative phosphorylation, is capable of forming Adenosine Triphosphate (ATP). ATP is more or less considered a “unit of currency” in energy transfers occurring within the cellular environment and is indispensable for metabolic reactions.

\textsuperscript{35} ATP synthase- A transmembrane enzyme that acts on the energy created by the electron transport chain to synthesize Adenosine Triphosphate (ATP) from Adenosine Diphosphate (ADP) and an inorganic Phosphate.

\textsuperscript{36} Anaerobic- Referring to an organism, environment, or cellular process that exists in the absence of molecular oxygen.
Both of these processes are present in every animal, including humans and leeches. We propose that James Marcus took from the leech genome the genes which code for the enzymes in these processes, as well as genes for hormones which up-regulate these processes, and expressed them in the T-Virus. Marcus would have had to place them among the early-activating genes of the virus, allowing expression of these genes to begin almost immediately, even before the virus integrates into the host genome. When expressed in the host, these enzymes and hormones would allow the cells to continue to produce energy even as circulation shuts down and cells start running out of oxygen. The result would be something discussed in Wesker’s Report II – a virus that keeps its host alive long enough for the virus to spread to others.

These cells might continue to obtain nutrients from the lysate\(^{37}\) of the dead cells and tissues surrounding them. This material would be mostly protein, and it turns out that leeches use degradation of protein as an energy source even in the absence of oxygen\(^{xxix}\). This would, incidentally, speed up their decomposition and increase the need for them to consume animal tissue. If the T-Virus also contains genes for various amino acid deaminase\(^{38}\) enzymes, then the infected cells could produce ammonia as they break down the proteins of dead cells for energy. The ammonia would help to reduce the acidity produced by increased glycolysis.

If each cell continues to obtain nutrients from its surroundings, and continues to function in the absence of oxygen, then the importance of the heart, lungs, and circulatory system are drastically reduced. Not only can the zombie function with these organs operating at a reduced level, the zombie can keep going even if these organs are severely damaged. A human grievously injured by zombies can rise up as one himself, and a zombie can continue to seek prey after taking half a dozen bullets in the chest, as we see throughout the Resident Evil series.

Brain damage

Zombie behavior still needs to be explained. Zombies may be persistent, but they’re dumb as bricks, and their shambling indicates a loss of motor coordination. Both of these traits suggest brain damage. It is easy enough to envision the T-Virus causing damage, through a combination of the action of the superantigen and T-Virus-specific causes related to this virus’s stronger promoters, which we will discuss in more detail later. For now, we can say that these stronger promoters might lead to cell death from more rapid viral replication, causing cell membrane depletion as the virions are exocytosed. In addition, these stronger promoters would up-regulate the Progenitor genes which themselves up-regulate metabolism, causing greater metabolic stress on the brain than Progenitor would on its own.

That explanation, of course, depends on the T-Virus getting into the brain – but the brain has a defense mechanism.

The blood-brain barrier is a layer of endothelial cells\(^{39}\) surrounding the capillaries and blood vessels in the brain, which allow only nutrients and oxygen to enter the cerebrospinal fluid\(^{40}\) and only waste products and CO\(_2\) to leave it. There are viruses which can infect the brain; rabies gets around the blood-brain barrier by traveling into the brain through peripheral nerves. The problem is that this mode of infection is slow, taking months to manifest. It simply could not work in a virus which causes behavioral changes in minutes.

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37 Lysate- The material formed by the lysis of cells.
38 Amino acid deaminases- Enzymes which act by breaking down amino acids, the structural units of proteins.
39 Endothelial cells- A specialized group of epithelial cells which line the interior of all structures within the circulatory system.
40 Cerebrospinal fluid- A clear fluid which surrounds and cushions the brain and spinal cord.
Fortunately, viruses in the Progenitor family (including the T-Virus) infect all tissue types, not just nerve tissue, which should allow them to enter the tightly joined cells of the endothelial tissue. From there, they might be shed into the cerebrospinal fluid by exocytosis, or they might lyse the cells of the endothelium, permeabilizing it and allowing bloodborne T-Virus to enter the brain in large quantities.

Simple brain damage is enough to explain shambling and loss of cognitive faculties, but cannibalism is a bit trickier. We initially approached cannibalism in three ways. First, we already propose that the Progenitor Virus increases aggression by inhibiting monoamine oxidase A. That could partially explain a zombie’s urge to attack people, but not to eat them. We have proposed that Progenitor increases production of growth hormones; it may stimulate growth hormone in part by up-regulating production of the hormone ghrelin\textsuperscript{41}, which is known to increase feelings of hunger.

Second, we considered the role of the leech DNA in the T-Virus. We have found that leeches have a peculiar capability to regenerate nerve cells\textsuperscript{xxx,xxxi}, and we thought James Marcus might have put the genes responsible for this regeneration into the T-Virus – the Leech Growth Records in \textit{Resident Evil 0} indicate Marcus’s leeches became more intelligent after he infected them with the T-Virus, and over-expression of these genes may have been the cause. If these genes play a role in zombie behavior, then new nerves might grow to replace damaged brain tissue in the zombie. However, this growth would not necessarily match the neural patterns which were in place before, and might result in unusual behavior, including cannibalism. If there is a pattern to this growth, we might see a tendency toward cannibalism in everyone infected with the T-Virus. However, that theory depends on the nerve-growth genes being among the early-expression genes of the T-Virus, and nerve growth could potentially take a long time – much longer than the few minutes required for the T-Virus to turn a person into a zombie.

Our third and favorite option involves a sort of psycho-behavioral mash-up. It is possible that the T-Virus preferentially attacks certain parts of the brain, for reasons we don’t understand. What might be left might be enough to keep some basic functions going, as well as a few instinctual behaviors. These might include the drive to feed (obviously), the ability to recognize other individuals, and a competitive instinct directed toward these other individuals. Essentially, zombies can see competition, and are driven to eat. In a zombie’s messed-up brain, all of this comes together as a drive to eat the competition.

Incidentally, it seems that zombies do not recognize other zombies as competition. We suspect the decomposition of a zombie’s skin might prevent it from releasing basic olfactory cues, such as pheromones and MHC proteins\textsuperscript{42}, which another zombie might detect and interpret as human.

\textbf{Infection in other animals}

Many \textit{Resident Evil} games have shown us dogs and crows infected with the T-Virus. \textit{Outbreak: File #2} showed us infected hyenas, tropical birds, lions, and an elephant as well. According to the \textit{Resident Evil Archives}, Eliminators are also created through infection by the T-Virus, not the

\textsuperscript{41} \textbf{Ghrelin} - A hormone primarily secreted by cells of the stomach’s fundus to induce feelings of hunger.

\textsuperscript{42} \textbf{MHC proteins} - A set of cell surface proteins present on the cells of all vertebrate animals which serve an important role in both defense and diversity of the immune system as a whole. Recent data indicates that not only can MHC be discerned via olfaction but that it also plays a role in mate selection.
Progenitor Virus, as the B.O.W. Report in Resident Evil 0 would suggest (it may be that Eliminators were actually based on earlier Progenitor experiments described in the B.O.W. Report). All of these animals exhibit necrosis, like humans, and all probably also exhibit the early metabolic restructuring which allows infected humans to keep going. What separates these animals from human zombies is that they do not lose any of their running speed or motor coordination.

We have described earlier that the proposed superantigen in the Progenitor virus may have come from a recombination event involving a human endogenous retrovirus. It may be that, before that retrovirus became endogenous to the human genome, it was only capable of infecting humans. If that was the case, its superantigen might have evolved a specificity for human immunoreceptors, and might not provoke a severe immune response in other organisms.

Wesker’s Report II mentions that Wesker and Birkin attempted to modify the T-Virus to increase its lethality. If our superantigen is the key virulence factor, it may have been modified in the T-Virus for broader affinity to its receptor type. While this effort seemed to be ineffective in increasing the morbidity rate in humans, this broader affinity might permit the T-Virus to cause necrosis in animals, even though Progenitor has no lethal effects in animals that we are aware of. However, the superantigen might still have reduced overall effect in nonhumans. This reduced effect might preserve enough of an animal’s brain tissue that it could retain full motor coordination. This explanation suggests a low importance for the other brain-damage factors in T-Virus infection, such as increased replication and metabolic stress on the brain.

Another hypothesis is that the T-Virus preferentially replicates in the tissues of the frontal lobe, perhaps due to higher numbers of GLUT receptors, or a GLUT type with a higher affinity for the virus. That would explain why the T-Virus obliterates the human capacity for reasoning, but it only reduces, not destroys, motor function, sensation, and physiological functions. Humans have a lot of frontal lobe, giving the T-Virus a lot more room to replicate, with the result that, when all’s said and done, the cerebrospinal fluid in a human skull contains a much higher titer of the T-Virus than an animal skull would. This higher concentration of virus puts the rest of the human brain, including the motor cortex, in danger of a destructive lytic infection rather than mere, gradual latent infection. Animals retain their motor functions, which is why Cerberus are among the biggest pains in the ass in the series.

We consider giant insects to be a result of mutation rather than mere infection, and we will get to them later.

**V-ACT**

As we’ve stated, we believe that the T-Virus turns people into zombies through two mechanisms: damage caused by replication and superantigen production; and early transcription of some leech proteins. We haven’t said anything about viral integration, which is one of the key features of any retrovirus and the cause of some of the Progenitor Virus’s most drastic effects. The effects of viral integration really come into play when a zombie undergoes further metamorphosis, developing into a V-ACT, or Crimson Head.

The Crimson Heads are apparently derived from a mutant strain of the T-Virus which developed in a researcher’s body after he was accidentally exposed, according to the V-ACT
We've highlighted the phalanges. You're welcome.

file in the *Resident Evil* remake. Umbrella saw potential in the new strain; they froze the infected researcher’s body and produced stocks of the mutant virus. Interestingly, this story has a real-world precedent – during the Cold War, a Soviet biological weapon researcher named Dr. Nikolai Ustinov was accidentally infected with Marburg virus, a cousin of Ebola. The strain which grew in his body, and eventually killed him, was far more potent than normal. His colleagues took samples from his corpse and used the new virus, Marburg Variant U, in subsequent bioweapon experiments.

But let us return to the T-Virus. After a zombie carrying the V-ACT strain is incapacitated, it can apparently regenerate, becoming stronger and faster, and sporting sharp claws and red skin. This regeneration may be stimulated by SAPK pathways – stress-activated protein kinase pathways. SAPK pathways are mechanisms used by cells to survive hard times like starvation and heat shock, and pretty much every organism has them. These pathways may in turn stimulate T-Virus-transformed cells to secrete hormones to trigger cellular growth throughout the body, leading to systemic transformation.

The regeneration seen in V-ACTs may be the result of a combination of two factors. First, the T-Virus contains most or all of the genetic code present in the Progenitor Virus, which would include the genes responsible for increased metabolism, healing, speed, and strength. Second, the T-Virus also contains some leech genes, possibly including those which give leeches and other annelids superior powers of regeneration (everyone has heard at some point that an earthworm can survive being cut in half?). These factors would not only allow a zombie to get back on its feet, but might even explain how it recovers some of the strength of an uninfected human. We also know that leeches have the capability to regenerate damaged nerves, in part through increased expression of matrix substrate molecules like laminin and tenascin; genes relating to this process might also be present in the T-Virus. These genes might repair damaged brain tissue, giving the zombie some of the motor coordination destroyed earlier in the infection and allowing it to run rather than shamble.

If this mutant strain of the T-Virus included stronger promoters in the SAPK pathways, then the expression of these regenerative genes and growth factors would be far in excess of what is seen in the Progenitor Virus. This overexpression might lead to the reestablishment of epiphyseal plates in some long bones. Given the absence of epiphyseal plates in the bones of adults, if these plates do reform, they would probably do so on the bone surface instead of in the metaphyseal regions near the ends of the bone, and they would probably form in areas not occupied by ligaments, tendons, cartilage, or synovial fluid. The most promising locations are therefore the tips of the third-row phalanges. Bone growth in these areas leads to the development of what look like claws emerging from the skin of the fingers and toes. Bone growth in particular could result from increased secretion of osteocrin or decreased expression of NPR-C receptors, probably as a secondary effect of overall metabolic and growth-factor up-regulation.

Rapid reestablishment of the metabolism, and repair of the heart, would restore blood pressure, potentially leading to excessive blood seepage through the ruined arterioles and capillaries of the skin. If the lungs are reactivated, this blood will be oxygenated and will be bright red, giving the Crimson Heads their distinctive coloration.

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43 **Epiphyseal plates**- Located within the metaphyses (the wider part at the end of a long bone’s shaft), these growth zones comprised of hyaline cartilage are responsible for the growth of long bones and remain present until early adulthood.

44 **Synovial fluid**- A transparent, viscid fluid secreted by the synovial membrane and contained in joint cavities, bursae, and tendon sheaths.

45 **Phalanges**- The bones of the fingers and toes.

46 **Arterioles**- A small vessel that conveys blood between an artery and a capillary bed.
Finally, we’d like to note that the V-ACT process occurs primarily after a zombie has been incapacitated by injury. This fact parallels the effectiveness of the Wesker Virus (and likely the Progenitor Virus) when it is administered prior to severe injury. Once again, stress hormones and signaling compounds released in response to injury might jump-start transcription and expression of Progenitor and T-Virus proteins. Javier’s modified zombies in *Dark Side Chronicles* seem to express these traits constitutively, though at a lower level, possibly due to infection with a different strain of T-Virus.

We’re guessing that V-ACT stands for Viral ACTivation. It’s simple, it’s elegant, and it’s probably right.

**Lickers**

Crimson Heads do not appear in the later Raccoon City outbreak featured in *Resident Evil 2*. Instead, a new breed of secondary mutation is introduced – the Licker. The *Resident Evil Archives* and the Umbrella Top Secret File in *Survivor* both indicate that Lickers are in fact the result of further transformation in zombies. The *Biohazard 3 Last Escape Official Guidebook*, which is unfortunately available only in Japanese, claims that Lickers are formed from a metabolic overhaul which occurs when a zombie begins to starve to death. It is quite possible that in this new strain of T-Virus, the regulatory regions of the SAPK pathway have been modified to remain dormant until a majority of the body’s cells begin to experience metabolic stress in the form of starvation. As a trade-off, the effects of the transformation are far more pronounced.

As the muscles continue to grow, they expand and eventually tear through the subject’s rotted skin and clothing. This muscle growth may be due to increased expression of FHL1 protein and/or the cofactor NFATc1 which binds to it\(^{xxiv}\). Reduced expression or inhibition of the hormone myostatin, coupled with increased expression of follistatin, could also increase muscle mass\(^{xxxv,xxxvi}\). It’s worth noting that, since we don’t see this kind of increased muscle mass in most Progenitor subjects, that this effect may well be due either to stronger promoters or to leech genes present in the T-Virus. As in Progenitor, increased fatty acid catabolism would break down fat for energy, preventing it from building up due to metabolic up-regulation as the muscles do.

The “claws” on the fingers and toes continue to grow. Perhaps the *osteoblasts*\(^{47}\) of the new growth regions in the phalanges migrate over the surface of the *metacarpals*\(^{48}\) and *metatarsals*\(^{49}\), and the hands and feet grow into the enormous talons we see on Lickers. New osteoblasts might aggregate on the surfaces of other bones, such as the *scapulae*\(^{50}\), forming not epiphyseal plates, but “osteoblastic laminae”\(^{51}\). Bone growth in these areas

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\(^{47}\) **Osteoblast** - A bone-forming cell which deposits and mineralizes osteoid, a form of collagen.

\(^{48}\) **Metacarpals** - The part of the hand between the wrist and the fingers containing five long bones.

\(^{49}\) **Metatarsals** - The part of the foot between the ankle and the toes containing five long bones.

\(^{50}\) **Scapulae** - Known to laypeople as the shoulder blades, the flat, triangular bones located under the shoulders.

\(^{51}\) **Laminae** - A general term for a plate or layer consisting of a composite material, in this case the layer covering bone.
might result in the appearance of the subject’s bony shoulder plates. Osteoblastic laminae may also develop on the pelvis, changing its shape and giving the subject’s legs a splayed, reptilian posture.

All the minerals needed for this bone growth have to come from somewhere, and presumably they come (in part) from the calvarium, the top of the skull. As osteoclasts\textsuperscript{52} eat away at the cranial dome, new brain tissue begins to grow, spurred by leech genes which regulate nerve regeneration. The eyes are lost as that part of the skull is degraded. This nerve development may also cause the increase of olfactory receptors in the nose and perhaps even the paranasal sinuses, and new follicle cells may begin to grow in the cochlea, giving the Licker a more sophisticated sense of smell and hearing.

Lickers may gain their distinctive tongues through the action of muscle growth factors acting on the intrinsic muscle\textsuperscript{53} of the tongue. Since these intrinsic muscles have their origin and insertion anchored to the same bone, they may simply have more room to grow than other skeletal muscles.

The Evolved Licker

A peculiar variant of Licker can be found in the Underground Research Facility in Resident Evil 2 and Dark Side Chronicles. Termed “Evolved Lickers,” these B.O.W.s are distinguished from their cousins by enlarged, sickle-like anterior claws and greenish coloration. Naturally, they are also slightly tougher than the garden variety.

The sickle claws may be a consequence of increased sonic hedgehog expression. We’ve previously suggested a role for sonic hedgehog in relation to vision and healing, but it also has a role in limb development. If this gene is overexpressed in the limbs, Lickers might experience a corresponding increase in FGF4 secretion, which could act to promote continued elongation of the limb, even beyond the formation of the claws seen in normal Lickers. In the absence of other factors, such as HOX8 and ALX4, we wouldn't see any anterior/posterior polarization; the result might be a single growth from the region of the wrist, failing to differentiate into fingers. Of course, other B.O.W.s, such as Hunters and most Tyrants, form fairly standard-looking claws. Furthermore, in the Evolved Lickers, while the middle claw grows to a larger size than in normal Lickers, the other claws are actually smaller than in normal Lickers, suggesting they never reached full size in the first place.

The Evolved Licker also has a green, pebbly skin. The regeneration of skin might be related to a mutant GJB2 gene. We described GJB2 and its protein product Cx26 in the section on hearing and sight in the Progenitor essay, but as we noted there, it also has a function in skin healing. However, in order for GJB2 to promote skin healing, large amounts of skin must already be present – and this is clearly not the case in normal Lickers. Furthermore, normal T-Virus variants cannot easily explain the green coloration.

We had once believed that Evolved Lickers were merely older Lickers which were further modified by the mutagenic properties of the T-Virus; however, the factors mentioned above seem to discredit this explanation. It’s also worth noting that, of the many, many Lickers seen in Resident Evil 5, none of them have developed these traits.

We propose that the Evolved Lickers did not actually “evolve” from normal Lickers, but rather, were created deliberately by Umbrella researchers. Direct injection of FGF4 into the wrists early in

\textsuperscript{52} Osteoclasts- A bone cell associated with the absorption and removal of bone.

\textsuperscript{53} Intrinsic muscle- A muscle whose origin and insertion are both in the same region.
Licker development might cause the growth of the sickle claws while inhibiting the growth of the other claws. The use of a T-Virus strain carrying reptilian transgenes – similar to those used to produce Hunters – might explain the green, pebbly skin texture, assuming the researchers found a way to keep the skin from necrotizing completely. Inhibition of the superantigen might allow the skin to be preserved.

**The Regis Licker**

Compared to their brethren in *Resident Evil 2*, the Lickers of *Outbreak* appear to be slightly less-developed. Their hands also seem to retain human-like articulation with digits that resemble fleshy spindles. It could be that they’ve transformed more recently and, as juveniles, would thus display less musculoskeletal development. The Lickers in *Resident Evil 2*, on the other hand, have already completed their maturation process, hence their heavily-muscled bodies and enormous bone claws. Had they not been killed by the cast of *Outbreak*, the Apple Inn population would have probably matured into sturdy Lickers, claws and all, as the days went on. However, one particular Licker stands apart from them.

The Regis Licker appears to have diverged from regular Lickers considerably in its development. Found in *Outbreak*, the Regis Licker seems to have a longer tongue than normal Lickers, but otherwise seems less developed than its brethren. It is less muscular than other Lickers, and most of its skin is intact, although it has a red hue. The Regis Licker has retained its eyes, hands, and the top of its skull, and even appears to have hair on its scalp and shredded clothing on its body. It also appears to have some command over other Lickers. It is hard to say whether or not its eyes are functional, but the Regis Licker does seem to have a heightened sense of hearing, as shown by its reaction to loud sounds. Unlike other Lickers, Regis appears to display numerous keloids and/or large osteomas growing on its right arm.

We have considered several explanations for the Regis Licker’s uniqueness. It may be that the organism was once a human who possessed innate immunity to the Progenitor superantigen, like Albert Wesker. Such immunity would protect her skin from the worst aspects of the T-Virus, but the virus’s stronger promoters would still cause increased replication in her brain and metabolic stress on brain cells, leading to brain damage and violent behavior. Alternately, she may have been a zombie which transformed into a Crimson Head through injury, and which later began to starve, initiating the Licker transformation. This two-stage transformation might have exacerbated certain factors, like the length of the tongue and keloid/osteoma growth. The revitalization of certain tissues during the V-ACT process may have prevented the wholesale loss of the skin, calvarium, and eyes.

It’s worth mentioning that the word “Regis” itself bears connotations of royalty as a Latin term, since this organism is in fact able to command other Lickers to some extent, suggesting the imminent emergence of

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54 **Keloid**- An irregularly-shaped, elevated scar resulting from the formation of excessive amounts of collagen during wound healing.

55 **Osteoma**- A benign, slow-growing tumor comprised of compact bone.
eusociality\textsuperscript{56}. At minimum, the Lickers of the Apple Inn demonstrate two of the milestones necessary for the evolution of eusociality – congregation and cooperation\textsuperscript{xix}. Perhaps the Regis Licker and the eusociality of this particular Licker enclave parallel the leeches of \textit{Resident Evil 0}. There are no known leech species to date which exhibit anything resembling the hive-mind of Marcus’ leeches, suggesting this unique behavioral trait emerged post-infection to increase chances of survival. By extension, this collective mentality could also emerge in higher organisms. As with the leeches, however, prolific brain growth would precede any expression of these new social patterns, a prerequisite clearly met by Lickers. But what accounts for the preeminence of Regis?

As it were, we know from \textit{Resident Evil 5} that Lickers were infertile until modified with Progenitor. Such infertility would naturally stem from the egregious conditions the body must withstand in the transformation from zombie to Licker. And this is where the Regis Licker’s relatively intact physical features come into play. Based upon speculation (and ignoring her hanging entrails), the aberration of V-ACT in Regis has led her to regain reproductive functions; in that regard, Progenitor and its derivatives may have a role in up-regulating the dynactin p62 gene. Dynactin p62 is present in all eukaryotic organisms; it plays a role in cell division (making it a useful gene for Progenitor to up-regulate)\textsuperscript{xxviii}. However, it also plays a role in the development of queen bees\textsuperscript{xxxix}. Up-regulation of this gene by Progenitor and the T-Virus may account for the increased fertility experienced by females of such disparate species as monkeys, leeches, and V-ACT humans. It still stands to reason that the Regis mutation, as a genetic factor, would remain exceedingly rare; the Licker β in \textit{Resident Evil 5} probably would not have become fertile without the benefits of Progenitor inoculation.

Another possibility for up-regulation involves the insulin-like signaling network, or IIS. This pathway has been shown to be necessary for growth and development – again, making the hormones of this pathway useful targets for enhancement by Progenitor. Recent studies have shown that this pathway may also be involved in the development of queen bees\textsuperscript{xl}. A particular adaptor protein, insulin-receptor substrate, has been shown to be important in this process – and it’s also expressed in mammals\textsuperscript{xli}. However, while the dynactin p62 gene and the IIS pathway may explain the Regis Licker’s matriarchal tendencies, they rest upon other hypotheses to explain her uniqueness in that regard.

Regis, as the lone source of fertility, would now occupy a role equivalent to a queen bee or queen ant wherein she remains largely inactive and is defended but otherwise exerts no control over the colony. Maybe Regis secretes a hormone which stunts the growth of the surrounding Lickers and reduces them to protecting her. While this is consistent with the reproductive regulation imposed by queens of bees and ants, we’ve yet to determine a viable mechanism through which this would occur.

In nature, eusociality requires a rather specific series of evolutionary adaptations. It was long thought that kin selection played a major role – kin selection being the theory that social organisms will expend energy to help their genetic relatives, but not unrelated or distantly related members of their species. There was, of course, no time for this kind of selection for Lickers in Raccoon City, so it is fortunate that some mathematicians have now suggested that kin selection may not be necessary after all\textsuperscript{xlii}. It’s been proposed that natural selection alone may account for the emergence of eusociality – in particular, random genetic recombination may be sufficient to produce “eusociality genes.” While the Raccoon City disaster did not allow enough time for proper natural selection, genetic recombination was extremely common during the T-Virus outbreak.

\textbf{Licker β}

\textsuperscript{56} \textbf{Eusociality} - A hierarchal form of social organization utilized by certain organisms wherein a reproductive division of labor, overlapping generations, and cooperative care all figure prominently.
One other Licker type appears in *Resident Evil 5* – the Licker β, created when normal Lickers were injected with the Progenitor Virus. According to the file Tricell Researcher Miguel’s Journal – No. 1, the Licker β is only a slight improvement over the original Licker – the new model has an improved sense of smell, and they have gained the ability to reproduce. Miguel does not mention certain other differences which can be seen in game play. Judging from their appearance, they seem to have increased muscle mass over normal Lickers, and they are a slightly greater danger to the player. They have developed a tendency to attack in groups, making them far more dangerous than the loners of *Resident Evil 2*. Finally, their hearts are exposed, creating a weakness which apparently did not exist before.

It is perhaps to be expected that the Progenitor Virus would have milder effects on creatures which had already been exposed to the T-Virus; after all, creatures infected with the T-Virus already carry the genes of the Progenitor Virus in their genomes. However, multiple copies of genes can increase expression of gene products, leading to a more prominent phenotype\(^57\) compared to a single gene. As we have indicated above, the increased strength and muscle mass can be attributed to general increases in growth factor secretion brought about by the Progenitor Virus. Progenitor genes might also lead to an improved sense of smell through establishment of new olfactory receptors in the paranasal sinuses, as we proposed for other Lickers.

The new capacity to breed might be a result of general hormonal up-regulation leading to increased ovulation. The mere fact that these Lickers can breed may account for their tendency to attack in packs; if they are born in litters, they may establish familial bonds with their litter-mates, and thereafter they would operate somewhat like a pack of dogs or wolves.

The most troubling trait of the Licker β is the exposed heart. We had originally considered that this trait might share a common cause with the exposed hearts of some Tyrants. However, certain aspects of the Tyrant hearts have convinced us that another mechanism may be at work – a mechanism which will be elucidated in the next Report. The exposed heart of the Licker β may instead result from the fact that this creature can reproduce. Since this organism now carries two copies of the Progenitor genome, the expression of certain growth factors must be extreme. The organs of the thoracic cavity may develop particularly fast, forcing the ribcage apart at the embryonic stage, before cartilaginous joints can grow strong enough to anchor the ribs to the sternum. The developing heart would displace the sternum, growing to prominence in the gap between the ribs on the left and the ribs on the right.

**Mutation in insects**

The following sections on the T-Virus will only cover animals which developed mutations due solely to exposure to the virus. We will not cover B.O.W.s like Hunters or Tyrants here, since their creation must be far more complicated. Fortunately for us, that mostly leaves insects and reptiles growing to enormous sizes.

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\(^{57}\) **Phenotype** - The expression of a specific trait, such as stature or blood type, based on genetic and environmental influences.
Upon realizing that a centipede this large should not exist, Rebecca decides to investigate more closely. Source: Resident Evil 0

We see a variety of giant arthropods in Resident Evil. Most of these are, fortunately for us, merely giant versions of normal creatures, like the Stinger, the Centurion, and the Plague Crawlers from Resident Evil 0, the giant spiders (including the Black Tiger and the Black Widow) from other games, the moths from Resident Evil 2 and Code: Veronica, and the wasps that appear from time to time. We have explained before in the section on the Progenitor Virus that the virus may stimulate the secretion of prothoracicotropic hormone, which stimulates molting and thus permits greater growth. The growth factors generated in a Progenitor infection probably assist with this growth.

Sometimes Capcom throws us a bone and provides insects which are large, but not freakishly so – like the wasps in the original Resident Evil and its remake, and the roaches in Resident Evil 2. Insects that large and larger have actually existed millions of years ago, when the atmospheric oxygen content was high enough to support themxliii. However, some arthropods, such as the Stinger, the Centurion, the Black Tiger, and the Black Widow, grow to truly obnoxious sizes. Most people know that insects simply can’t get that big, for a variety of reasons – their legs won’t support their body weight, and more importantly, their open circulatory system58 and spiracles59 can’t oxygenate the tissues of a body that largexliiv. Objection one is easy to counter; we speculated in the above essay on the Progenitor Virus that the virus apparently replaces myosin light chain proteins with a stronger variant. The growth hormones generated by Progenitor infection (and overproduced by the strong promoters of the T-Virus) result in more muscle and thicker chitin60 layers relative to the diameter of the legs and body. These factors give the insects stronger legs and carapaces, allowing them to carry their weight.

The second objection is nullified by the leech genes in the T-Virus. We have already described how these genes permit a human body to function in spite of reduced oxygen availability. Perhaps insect tissues also benefit from these genes, allowing the insect to grow far beyond the ability of its anatomy to keep its tissues oxygenated.

These factors may also account for the properties of the Gulp Worm in Code: Veronica, which was created from a worm; however, the Resident Evil Archives indicate the Gulp Worm is also a product of genetic manipulation. The Archives do not specify what kind of worm was used to create the creature. Translations of Capcom Japan’s Code: Veronica official website indicate that the Gulp Worms were created using earthworm genes; however, we suspect genes from other annelids might be involved as well. The European medicinal leech, Hirudo medicinalis, has jaws resembling that of the Gulp Worm.

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58 Open circulatory system- A circulatory system in which fluid called hemolymph bathes the tissues and organs directly so that there is no distinction between the circulating fluid and the interstitial (tissue) fluid.

59 Spiracles- Small orifices on arthropods which allow air into their respiratory system.

60 Chitin- A structural polysaccharide which serves as the primary constituent of arthropod exoskeletons.

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The Grave Digger (and its offspring, the Sliding Worms) are described as mutant arthropods in the *Resident Evil Archives*, but they certainly don’t look like any arthropods we’re familiar with – no adult arthropods, anyway. After a bit of consideration, they remind us a little bit of grubs. It seems to us that some larval insect, perhaps a grub or a maggot, was infected with the T-Virus. The virus spurred production of growth hormones, and the organism grew to enormous size; at the same time, these hormones threw off the hormonal balance of its normal growth pattern, or viral integration interrupted a gene necessary to metamorphosis, so that it never metamorphosed into an adult insect. The virus essentially caused a **progenetic** mutation, which was inherited by the creature’s offspring. If the initial larva (the Grave Digger itself) was of a beetle, that would explain the creature’s affinity for burrowing through the ground.

A couple of other cases of insect mutation are worth mentioning. The *Resident Evil Archives* describes the Brain Suckers and Drain Deimos of *Resident Evil 3* as being a result of fleas becoming infected and mutating to large size. However, they appear freakishly deformed, especially the Brain Suckers. The *Biohazard 3 Last Escape Official Guidebook* describes the Drain Deimos (and possibly the Brain Sucker) as being a result of superinfection – a condition in which a cell is infected by the same virus more than once. Superinfection would result in genes being expressed far in excess of normal conditions, and since the Progenitor Virus up-regulates a variety of growth hormones, superinfection could cause body parts to grow out of proportion. This superinfection was apparently caused when the insects took blood from viremic animals, exposing themselves to a massive viral load. Additionally, the *Guidebook* states that, by taking in the blood of multiple animal species including reptiles, the creatures which would become Brain Suckers exposed themselves to virus-assisted genetic recombination, contributing to their monstrous appearance. The *Guidebook* also states that the organisms grew to their enormous size through **exuviations** – that is, molting.

**Mutation in other animals**

We also see extreme growth in some reptiles, such as the alligator in *Resident Evil 2*. We do not believe the gator was a result of mutation by the T-Virus – just a victim of circumstance. This gator very likely ate one of the giant spiders in the Raccoon City sewers, which, as we have described, are probably full of prothoracicotropic hormone. When this substance and its related family of **ecdysteroids** are injected into animals, including vertebrates, they also seem to grow, although there’s obviously a lot less molting involved. The gator got a huge dose of this hormone, grew to a size most sewer gators can only dream of, and ultimately died a Spielberg death.

The Yawn may also have grown to enormous size after eating an infected spider in the Arklay Mansion, or it may be a result of B.O.W. genetic tampering. If it did come about as a result of accidental infection, it probably would have had to eat several juvenile spiders before it could work its way up to adults.

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61 **Progenetic**- Pertaining to a developmental aberrancy of certain organisms wherein they obtain sexual maturity while permanently retaining their juvenile form, usually as a result of environmental or chemical stimuli.

62 **Exuviations**- Molting. We had to look that one up.

63 **Ecdysteroids**- A class of insect molting hormones which can also affect growth patterns in vertebral animals. Plants and other invertebrates have also been shown to possess functional analogs of the ecdysteroids.
The Lurkers and the Giant Bat in *Resident Evil 0* may have fed on Plague Crawlers. The bat’s use of echolocation suggests it was of a species which feeds on insects.

We will deal with the effects of the T-Virus on plants in future installments, since we believe that most or all of the infected plants we’ve seen have come about as a result of genetic tampering as well as T-Virus infection. Likewise, we will discuss the effects of the drug T-JCCC203 (mentioned in *Outbreak: File #2*) when we discuss these plants. Al Lester, the Axe Man, will also be considered at that time.

### Leeches

Leeches seem to have some unusual reactions to the T-Virus. They seem to come in three flavors; the leeches bred by James Marcus may be the first to appear chronologically, but the leeches found in and beneath Raccoon Hospital in *Outbreak* are simpler in both behavior and appearance, and will be discussed first. The Queen Leech will be discussed in the essay on B.O.W.s; though it was never created as a weapon, it seems bizarre enough to warrant special treatment.

The Giant Leech in the sewer beneath the hospital is easiest to explain. We have described several times that the T-Virus and its aptly named progenitor spur organisms to grow to unusual sizes. Apparently, the Giant Leech can also upchuck digestive fluids at its prey, but if normal leeches can secrete hirudin\(^{64}\) (an anticoagulant) into a host’s wound, we don’t see this as being much of a stretch.

Other leeches in the hospital grow only slightly larger than normal, but retain all other appearances. The only difference is their behavior – they are able to aggregate on a host and, to an extent, alter that host’s behavior. At present, we have only one hypothesis. We know from Leech Growth Records in *Resident Evil 0* that leeches infected with the T-Virus appear to get smarter and coordinate their behavior (due to mechanisms which will be explained shortly). If the leeches coordinate their behavior using hormones and pheromones, and they are massed around a host, perhaps getting into his sinuses and even his skull cavity, then their hormonal signals might have some influence on the host’s brain. The host might then be drawn to blood when the leeches smell it, and might try to attack individuals the leeches detect as prey.

We believe the Giant Leech and its brood are members of the species *Macrobdella decora*, the North American leech. This freshwater species is native to a large part of the United States, lives in ponds and slow-moving streams, and has a taste for mammalian blood – making it a good match for leeches invading the hospital through the sewers. It can have a greenish coloration which would be useful for explaining the hue of the Giant Leech as well.

### The Marcus leeches

The leeches bred by James Marcus have a more distinctive appearance and more distinctive behavior. The round organ in the center of their bodies is described by the *Resident Evil Archives* as an eye. Leeches, it turns out, do have organs called ocelli\(^{65}\), very simple light-sensitive organs which are evolutionary precursors of eyes.

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\(^{64}\) **Hirudin** - A peptide present in the salivary secretions of leeches that acts as an anticoagulant to facilitate its feeding.

\(^{65}\) **Ocelli** - The small, simple eyes of invertebrates.
If Progenitor-type infections increase general rates of fluid secretion, then the tissue surrounding one of these ocelli may have become swollen, eventually forming a primitive cornea\(^{66}\).

Unfortunately, we don’t know of any leech with a single, large ocellus on its back. Nor do we know of any leeches with big, scary mouths on their ventral\(^{67}\) surfaces. At this point, we must resort to hand-waving. We know James Marcus was manipulating leech DNA as part of his work on the T-Virus. Perhaps he created a species of modified leeches himself, and infected them with the T-Virus. The above explanation regarding ocelli may therefore be superfluous.

However these leeches came to be, we know from the Leech Growth Records that they became smarter after being infected with the T-Virus. We have stated before that the T-Virus probably contains genes relating to the regeneration of nerves. Since these genes came from leeches in the first place, the addition of extra copies via T-Virus infection led to overexpression. These overexpressed genes stimulated the formation of synaptic\(^{68}\) connections and proliferation of nerve stem cells. Their early cannibalism, described in the Leech Growth Records, is probably due to decreased monoamine oxidase levels – the same factors which triggered aggression in other organisms.

In short, these leeches became smarter, and (whether due to the effects of the Progenitor Virus or sophisticated genetic tampering) they have eyes. Therefore, they could see James Marcus – the one individual who fed them and cared for them, and (judging by his diary entries) probably sang to them and cooed over their incubators. It is likely that, in time, they began to react to his presence the way a dog reacts to a loving master, and their tiny leech brains pumped out endorphins\(^{69}\) when he was around.

As a result of their increased intelligence, the leeches also began to operate as a collective, implying some form of communication. We believe their communication is pheromone-based. Successive to this development, they may initially have begun to huddle together in large masses to conserve heat (cold-blooded animals do produce heat, but are not able to regulate their temperatures metabolically). The Resident Evil Archives states that they secrete an adhesive mucus layer over their cuticles to help them maintain a shape; this mucus may initially have aided in helping them conserve heat, and they may secrete it in response to some pheromonal quorum-sensing\(^{70}\) mechanism. Due to their (suspected) affection for Dr. Marcus, they may have unconsciously begun to mimic his form, suggesting the development of mirror neurons\(^{71}\) in the leeches’

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\(^{66}\) Cornea - The transparent layers which cover the iris and pupil of the eye.

\(^{67}\) Ventral - Pertaining to the underside of an animal that flies, swims, or in this case, slithers in a horizontal motion.

\(^{68}\) Synaptic - Pertaining to a synapse, the site of functional connection between neurons.

\(^{69}\) Endorphins - Endogenous opioid neuropeptides which temper pain perception through analgesic effects; in addition, endorphins are also released during periods of excitement and pleasure.

\(^{70}\) Quorum-sensing - A chemically-regulated coordination of behavior in a group of organisms of the same species, such as the simultaneous release of molecules controlling biofilm formation within a bacterial colony.

\(^{71}\) Mirror neurons - Neurons which fire both when an organism performs an action as well as when the organism witnesses that action performed by another, as though it was still performing the action; in essence, this strongly connotes the idea of learning through active imitation.
brains. If they are able to alter the protein content of the adhesive mucus they secrete, this control might allow them to mimic details of color.

Its form and likeness established as a superorganism, the leech swarm then moves en masse, similar to schooling\(^2\) as observed in fish. This involves each leech synchronizing its motion in a coordinated fashion to give the appearance of stalking after any unsuspecting medics or convicts in the area.

Based on their coloration, we think Marcus’s leeches may be *Hirudo medicinalis*, the European medical leech, or more likely, *Hirudo verbana*, a common impostor. Both would have been available to an…enthusiast like Marcus. However, the North American leech, as mentioned above, has stomach chambers which give it a peculiar shape when it ingests a full blood meal. This shape can also be seen in the Leech Charms in *Resident Evil 0*. We’re not prepared to make a clear determination on the subject.

**Transmission**

We would like to get back to some of the medical aspects of the T-Virus. We’ll start with transmission. Obviously, the T-Virus can be transmitted by bites, hitching a ride into a victim’s bloodstream through the zombie’s saliva. The small amount of virus presumably passed through bites means that the T-Virus must be able to replicate in human cells, unlike Progenitor. The inclusion of leech promoter elements in the viral genome may account for this new function. The T-Virus might be actively produced in the salivary glands; alternately, necrosis of the skin tissues in a zombie’s mouth dumps loads of virus-laden cytoplasm into the saliva. Either method will work fine. But *Resident Evil* has a tendency to get vague with T-Virus transmission, and there are a few other mechanisms which need to be discussed.

James Marcus had a habit of swarming places with his army of leeches, which would kill everything in their path. It’s how the Ecliptic Express was contaminated, and probably how the investigation team at the Management Training Facility was infected. However, plenty of people were left alive at the Arklay Mansion, at least long enough to write suicide notes and bemoan their slow transformation into something less than human. Marcus may have found a more covert way to spread the virus there.

It’s getting hard to count all the times someone has vaguely “spread” the T-Virus through some research facility or throughout an island, but it can be done in a few different ways. The most effective ways to spread a weaponized pathogen are as an aerosol (airborne fluid droplets) or as a powder – for viruses, often by drying in trehalose and grinding to a fine particle size, although enveloped viruses are not particularly hardy in air. However, both techniques require specialized equipment and no little technical expertise – the kind your average biologist doesn’t have.

\(^2\)Schooling - A biological phenomenon where a population of fish aggregate and proceed to swim together in the same direction and at the same speed in a synchronized fashion.
James Marcus probably contaminated the water supply to the Arklay Mansion. His leeches have easy access to any water supply through Raccoon City’s myriad sewers, pipes, and tunnels.

We know that Raccoon City was contaminated through at least three sources: zombies from the Arklay Mansion and Management Training Facility wandering into town; rats feeding on smashed vials in the sewers and spreading through the city; and contaminated waste from the P-12A incinerator facility seeping into the environment. These three factors explain both the existence of some infected individuals before the assassination of William Birkin on September 23, 1998 (as noted in several files in Resident Evil 2 and 3), and the sudden epidemic which occurred on the day of the assassination.

The patrons of J’s Bar in Outbreak are unlikely to have caught the virus from drinking water; their low viral titers at the beginning of the game suggest they were infected at the game’s start – and honestly, who goes to a bar to drink tap water? The rat which nearly trips Cindy Lennox seems to be a clue, but the mere presence of the rat could not have caused infection, since the T-Virus cannot be transmitted as an aerosol from one host to another, the way smallpox can. Most likely, the rat had been in the kitchen or back of the bar before coming out to say hello. While there, it could have scurried among drinking glasses or food items, its paws still sticky with the concentrated T-Virus from the vials in the sewers.

Vincent Goldman claims to have “spread” the T-Virus throughout Sheena Island in Survivor (or Gun Survivor, if you prefer). He may also have contaminated the water supply; it would be the simplest way to distribute the virus to everyone on the island. It is possible for Vincent to have attempted to use an aerosol or powder dispersal; however, Sheena Island was primarily a B.O.W. production facility and they likely weren’t manufacturing concentrated T-Virus in large enough quantities for aerosol dispersal. It’s quite likely they weren’t engaged in weaponizing the T-Virus as a powder at all.

It’s quite possible that Wesker’s assault on Rockfort Island utilized one or the other form of weaponized agent dispersal. He was already bombing the island; one or more of these bombs could have contained dried virus. However, there is a damaged vent found by Chris, who is led to speculate that the virus may have spread from there. If that vent led to some place where large amounts of T-Virus-contaminated liquid was being stored, treated, or used in some way, it is possible for a small amount of aerosol to have traveled through the vent system. Presumably the ventilation system would normally have HEPA filters in place to prevent accidental release, but these filters would have been damaged by the bombing. The amount of aerosol which might be released from that kind of accident would be insufficient to contaminate the entire island, however.

On the other hand, if Rockfort Island housed a large-scale T-Virus production complex (such as for the production of dried, weaponized virus), then it is entirely possible for the entire island to have become contaminated by a damaged ventilation system. There are real-life precedents for such accidents.

If Morpheus Duvall had the resources to build a missile silo, he probably filled his warheads with dried T-Virus, since it’s hard to generate an aerosol from an intercontinental missile. On the other hand, maybe he just filled
the warheads with concentrated T-Virus slurry straight from a bioreactor and hoped to contaminate the water tables of his target locations. It would be crude and inefficient, but it would be effective.

Sergei Vladimir presents a problem. He had to spread the virus on very short notice, ruling out contaminated drinking water. Despite what the movies would suggest, smashing a vial of concentrated virus is typically not enough to create an aerosol cloud. Since the Caucasus facility was, in part, a warehouse for Umbrella biological weapons, the facility may have contained dried virus stocks, which could easily be spread through a ventilation system. Alternately, Sergei could simply have released the B.O.W.s stored on-site, allowing them to infect his staff.

Certain sources, such as Japanese novelizations of dubious canonicity, suggest that it was Wesker, not Sergei, who was responsible for the outbreak at the Caucasus facility. It was explained in the Umbrella Chronicles Side B novel that Wesker had arranged for a disgruntled or semi-gruntled employee to spread the virus prior to Wesker’s invasion. This makes much more sense to us than Sergei deliberately infecting his own researchers just to slow Wesker down, but this novel also gives Wesker and Sergei weird telepathic powers over zombies, so we’re taking it with a few kilograms of salt.

The T-Virus outbreak at Harvardville Airport was staged by Frederick Downing for the benefit of General Miguel Grandé. As such, it is likely the virus was dispersed in a weaponized form such as an aerosol or an airborne powder. The Atmos Airlines plane which crashed at the airport could not have been the source of the infection, as it crashed after the first zombies appeared in the airport; this fact makes the infection on the plane harder to explain. This plane may actually have taken off from Harvardville. As passengers (including one WilPharma employee) began to experience symptoms, the plane may have turned back for an emergency landing, crashing when the zombified passengers killed the crew.

**Rate of infection**

The wildly disparate rates of infection we see throughout the series also need to be addressed. The time between exposure and full-blown zombification can range anywhere from ten days (as seen in The Keeper’s Diary in Resident Evil and its remake) to thirty seconds (as seen in the CG movie Degeneration). The T-Virus may cause rapid infection if it causes expression of genes such as the vaccinia virus genes A33 and A36, which prevent superinfection by repelling virions using actin tails. This mechanism has been shown to increase the rate of infection at least fourfold by minimizing redundant infection.

This variation may occur based on two factors: the dosage of the initial infection, and the proximity of the site of infection to major blood vessels and the central nervous system. The security guard in Degeneration was bitten in the throat, introducing the virus directly into the blood vessels of his neck. The zombie seemed to be chewing on him for a few seconds before killing him, rather than killing him by tearing his throat out in a single bite, and these multiple bites could have introduced plenty of
infected saliva into his wounds. From these wounds, the carotid artery would have carried the T-Virus directly into his brain, while the jugular vein would have carried the virus directly to his heart and, from there, to the rest of his body. As a result, he carries the honor of the fastest reanimation in *Resident Evil*.

It should also be noted that, when the T-Virus transmitted as an aerosol or airborne powder, symptoms may occur more quickly. The bacterium *Yersinia pestis* causes three kinds of plague; the aerosol-transmitted pneumonic plague has an incubation period of 1-3 days, while the flea-transmitted bubonic plague has an incubation period of 2-6 days. (The third kind, septicemic plague, typically resulted as a complication of one of the other two forms.) This may be because the lungs may offer a quick route through the pulmonary veins to the heart and therefore to the rest of the body. As described above, it is likely that the T-Virus was released in Harvardville Airport as an aerosol or powder.

It may also be possible that the T-Virus and Progenitor are able to form a biofilm-like complex on the surfaces of motile cells such as lymphocytes. This biofilm would consist of viral particles embedded in a matrix secreted by the infected cell itself, and it would drastically increase the chances of infection for any cell with which the lymphocyte comes in contact. This mode of transmission was only recently discovered, but at least one retrovirus uses it to great effect.

In contrast, the Keeper in *Resident Evil* took up to ten days to become a zombie. We know that James Marcus spread the virus through the Arklay Mansion, but the Keeper probably wasn’t infected by a leech bite, or he would have recorded it in his diary. Given the aquatic nature of leeches, and their easy access to water supplies, we suspect the T-Virus was spread through the mansion’s water supply. If this were the case, the Keeper would have been infected by a low dose, and the virus he ingested would be further attenuated by stomach acids and digestive enzymes. What little virus remained might have spread slowly through the epithelial tissue of the lumen of the intestines, gradually spreading through the body through capillaries and lymphatic vessels.

Before William Birkin’s sort-of assassination on September 23, 1998, the T-Virus had already begun to spread through Raccoon City due to contaminated waste leaking from the overtaxed P-12A disposal facility on the edge of town. This waste would have contaminated the water supply, resulting in slow infection as described above. This slow infection would explain the symptoms of Thomas, the chess aficionado described in the Watchman’s Diary in *Resident Evil 2*.

**The Dead Walk**

While we’re talking about the T-Virus spreading, we would like to clear up a common misconception. Viruses cannot infect dead tissue. No, not even the T-Virus. And they certainly can’t infect embalmed bodies. Viruses need living tissue in which to replicate – it’s the principle which sets them apart from all other forms of life. As a result, the scenes in *Resident Evil 3* and *Code: Veronica* where zombies burst out of their graves are going to require some explanation.

Regarding the cemetery zombies in *Resident Evil 3*, we can only speculate. It should be noted that the zombies don’t really emerge from proper grave sites, so these zombies probably weren’t in the ground before the Raccoon City outbreak. It’s possible that, in the early days of the epidemic – before the assassination of William Birkin – several individuals were mistakenly thought to be dead. It’s even possible that certain doctors under Umbrella’s thumb deliberately declared these people dead so they could be disposed of before they started moving again and started causing problems. If these people were homeless, they might be buried in the potter’s ground quickly, with no funeral service.
These would not be shallow burials, though. It would take something like the increasingly aptly named Grave Digger to break open their coffins and break up the earth around them, allowing them to claw their way to freedom.

The zombies in *Code: Veronica* are (slightly) easier to explain. The attack on Rockfort Island seems to have been going on some time – nearly everyone is infected or dead. After the initial salvo, the survivors may have had a moment to collect their wits and bury their dead as best they could. Knowing they were short of time, the survivors may have buried a number of bodies in shallow graves in the prison graveyard – especially the bodies of prisoners. These prisoners may already have become infected by the T-Virus during the attack, and were only apparently dead. The rain softened the dirt over them, and the scent of living human flesh – Claire Redfield – gave them reason to emerge *en masse*.

**Immunity**

According to Wesker’s Report II, William Birkin was never able to push the lethality of the T-Virus above 90%. Ten percent of individuals would simply never become infected with the virus.

We find it unlikely that this immunity stems from the same genetic factors as the ability to survive infection by the Progenitor Virus. First, we believe that Progenitor acceptance occurs at a lower rate – hundreds of Wesker Children were administered the experimental virus based on Progenitor, but only one survived. Second, if T-Virus immunity worked the same way as Progenitor acceptance, ten thousand super-powered T-Virus survivors would have emerged from Raccoon City, possibly taking up new roles as vigilante crime-fighters or supervillains.

No, whatever causes immunity to the T-Virus must also eliminate the possibility of the host gaining any benefits from the Progenitor Virus as well. One possible explanation relies on the leech DNA which makes the T-Virus special.

The human body has several natural ways to fight viruses. One method involves the infected cell recognizing the presence of a virus and simply dying before the virus can replicate and spread to other cells. We know from *Resident Evil 5* that the Ndipaya have been infecting themselves with the Progenitor Virus for a long time; the virus may have had plenty of time to evolve mechanisms to defeat this defense, as many other viruses have. We have also speculated that Progenitor incorporates genes from a human endogenous retrovirus and even some functional human genes – these genes would not be recognized as foreign by an infected cell. Leech DNA, however, is completely foreign. Its presence might just allow humans with exceptionally strong immune systems to detect the invading virus and induce apoptosis in the infected cells.

**Treatments**
Several vaccines and treatments against the T-Virus have been introduced over the course of the *Resident Evil* series. Naturally, they are not described very well; however, we may have enough information to deduce how these treatments might operate.

*Resident Evil 3* describes up to three different treatments, although only one is ever seen – and, for all we know, Capcom intended them to all be the same thing (in which case Capcom is wrong). The Mercenary’s Pocketbook describes a member of the UBCS receiving injections of antibodies against the T-Virus. These antibodies would either bind to the virus itself, preventing it from infecting cells, or it would bind to **antigen-presenting molecules** on infected cells, allowing the host’s immune system to recognize these cells and destroy them before they produce more virus. Though serum injections containing antibodies are normally short-term treatments, the ability to bind antigen-presenting molecules can force the body to recognize an infection, potentially priming the body to develop its own long-lasting immunity.

The antibodies given to the UBCS are probably **monoclonal antibodies**, which are used from time to time to treat individuals after exposure to a hazardous toxin or biological agent. Monoclonal antibodies can be harvested from B-cell hybridomas; they are more specific in their affinity to pathogens than polyclonal antibodies, which are extracted directly from the blood of an animal which has been exposed to a pathogen or toxin. The T-antibodies given to the UBCS are unlikely to be polyclonal; given the extremely high morbidity rate of the T-Virus, any animal infected would probably become viremic. Any attempt to extract polyclonal antibodies would therefore probably result in a product contaminated with virus, which would of course be useless as a treatment. It might still be possible to filter the virus particles out of the serum, but this process would be difficult, time-consuming, and expensive.

Also in *Resident Evil 3*, the Manager’s Diary describes a “liquid medicine” being given to employees at the disposal facility. This medicine may be the same as the antibodies given to the UBCS, or it may be an experimental **antivirus**. It may even have been the same as the vaccine Carlos Oliveira recovered from Raccoon Hospital, assuming the hospital’s basement laboratory was producing large amounts of the vaccine and not just individual doses. Beyond that, we really cannot describe this liquid medicine very well.

We are speculating here, but the liquid medicine may be a drug which inhibits the enzyme CD45. CD45 is an antigen-signaling receptor found on numerous immune cells, including B-cells and T-cells. Reducing expression of CD45 has been shown in laboratories to protect against diseases as varied as anthrax and Ebola, simply by reducing a normally destructive immune response. The same mechanism could be at work in the liquid medicine. We have suggested earlier that the T-Virus may produce a superantigen, which causes disease by overstimulating T-cells. By reducing expression of CD45 in the host’s T-cells, the drug may prevent the cytokine storm which we believe is the primary cause of brain-death in T-Virus victims.

The most important antiviral agent mentioned in *Resident Evil 3*, and the only one shown, is the one synthesized in Raccoon Hospital and given to Jill Valentine. In the Medical Instruction Manual, Douglas Rover of the Umbrella Medical Service describes the agent as a vaccine. Most vaccines are designed as prophylactic treatments – they are given to prevent disease, not to cure it. Vaccines stimulate the immune system’s B-cells to generate antibodies against an invading organism, and this can take days. When someone is already infected, there is a good chance the body will develop its own antibodies against the pathogen before the vaccine has time to take effect, making the vaccine something of a waste of time.

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73 **Antigen-presenting molecules** - The molecules which allow infected cells to display foreign antigens complexed with MHC proteins for recognition and destruction by immune cells.

74 **Monoclonal antibodies** - Chemically homogenous antibodies produced by a single group of immune cells, all derived from a parent cell, which target a specific antigen.

75 **Antivirus** - A specific class of drugs which acts to inhibit viral infection by exploiting certain stages of the replication cycle.
However, there are cases in which vaccinations can be effective forms of treatment even after infection. Some studies have shown that post-exposure vaccination can be effective against smallpox and even the Ebola virus, assuming vaccination occurs soon after the subject is infected, and long before the subject actually gets sick.

So it is possible for the Raccoon City Hospital vaccine to have saved Jill’s life after infection – but as we know from _Resident Evil 5_, Jill’s body harbored the virus for years afterward. Many viruses are capable of maintaining latent infection; herpes is famous for it. HIV and other retroviruses are also capable of maintaining latent infections; since their genetic material can integrate into the host’s DNA, these infections can effectively hide from the immune system indefinitely as proviruses, only reemerging as active infections at times when the immune system is weakened – for instance, during cryopreservation. The file on Jill in _Resident Evil 5_ states that when she was frozen by Albert Wesker in 2006, the T-Virus in her body was reactivated, apparently damaging pigment cells in her hair follicles and the irises of her eyes. Antibody production would have increased to fight the infection, as it had in 1998 when she received the vaccine. According to the file mentioned above, Wesker harvested such antibodies for use in his Uroboros Virus.

It’s also possible that the Rover vaccine was, strictly speaking, not a vaccine at all. It may have been an experimental antiviral drug designed to bolster the body’s own immune responses. One promising candidate involves RNA silencing, a mechanism used by plants – and apparently humans, according to new research – to fight viral infections. RNA silencing would prevent the synthesis of viral proteins – but just as importantly, it would reduce levels of viral RNA that a retrovirus would use to reproduce. One mechanism of RNA silencing, RNA interference, will be described a little later.

Two more antiviral agents are described in the _Outbreak_ games. In the first _Outbreak_ game, a reagent called Daylight is introduced. It was apparently developed in secret by a researcher and some a faculty member at Raccoon University. It is stated to require three components – P-base, V-poison, and T-blood. From these components, and the drug’s actual effects, we might be able to piece together a mechanism.

T-blood is easiest to identify – it is simply the blood of an organism infected with the T-Virus. Therefore, the virus must be used in some way to create the reagent. If Daylight were a normal vaccine, we would say the virus was used to make inert virus-like particles, which would stimulate the host’s immune system to recognize the T-Virus as an invader. This mechanism only works as a preventative measure, however – once a person is infected with the virus, the vaccine cannot be used to save them. We needed to find another mechanism.

It is possible that the virus was harvested by the incubator for its RNA. This RNA could be PCR-amplified and used to reduce
viral expression in an infected person through a mechanism called **RNA interference**\(^ {76} \). The short explanation is that double-stranded RNA enters a cell and is chopped by an enzyme called dicer into small fragments called **short interfering RNA (siRNA)**\(^ {77} \). These fragments bind to **messenger RNA**\(^ {78} \) produced by viral genes, silencing them. The bound mRNA is eventually destroyed by a system called the **RNA-induced silencing complex (RISC)**\(^ {79} \).

When the viral mRNA is silenced and destroyed, the cell stops making viral proteins and therefore stops making new virus. RNAi would basically stop the T-Virus infection in its tracks; following that, either the host’s immune system may destroy any infected cells, or the provirus in these cells becomes transcriptionally silent, as described above\(^ {lx} \).

We believe P-base is used to help PCR-amplify the viral RNA. In this case, the P would stand for “polymerase” and P-base would be a specially-designed, heat-stable, RNA-dependent RNA polymerase, which would be used as the enzymatic machinery to create more RNA molecules.

The final component is V-poison, which is extracted from a nest of mutant wasps. The V probably stands for “vespa,” which is Latin for “wasp.” Wasp venom is a veritable pharmacological cornucopia\(^ {lx, li, lii} \). It contains phospholipases, which can damage cell membranes; if used in very small amounts, these phospholipases might produce semi-stable pores in infected cells, allowing the pre-siRNA molecules to enter in large quantities. Wasp venom also contains histamines, which can dilate capillaries and make them more permeable, allowing the Daylight reagent to penetrate deep tissues more quickly, before the pre-siRNA degrades. An enzyme called hyaluronidase is also present in wasp venom; this enzyme damages a material called hyaluronic acid, which is a structural component of **extracellular matrix**\(^ {80} \). If the V-poison damages this extracellular matrix and makes it more porous, Daylight could penetrate the hard-to-reach tissues such as those in the bones and joints.

Two things need to be pointed out about the Daylight reagent: first, no university – no laboratory in the world – has an Easy-Bake Incubator which can isolate a virus from blood, harvest the RNA, PCR-amplify it to an amount which would silence transcription in trillions upon trillions of cells instantly, then calculate and add an extremely precise amount of wasp venom, all in thirty seconds. But if someone can believe half the other things we’ve proposed, that will have to be forgiven.

Second: yes, we know Thanatos exploded when it was given a dose of Daylight. No, we don’t know why, and no, we won’t even try to explain it.

In *Outbreak; File #2*, the Reagent Refinement File describes the reagent AT1521, which was apparently developed at the Umbrella Corporation’s Raccoon City Headquarters. According
to the file, the reagent only slows the growth of the virus, and does not eliminate the virus already present in a subject’s body. To us, this description sounded similar to what we have discerned about the Rover vaccine described above. According to Umbrella Chronicles, the supercomputer U.M.F.-013 is connected to all or nearly all Umbrella facilities worldwide and contains all or most of Umbrella’s research data. It may be that researchers at the Raccoon City Headquarters had access through U.M.F.-013 to the formula for the Rover vaccine produced by the Umbrella Medical Service, and attempted to refine the formula. They may even have used that supercomputer to sort through innumerable molecular variations on the Rover vaccine, looking for something with greater effectiveness.

Alternately, the AT1521 reagent may have been something like the real-world experimental antiviral compound LJ-001. This small molecule has been found to bind to viral envelopes, preventing viral entry into host cells. This mechanism makes it effective against a wide range of viruses, from Ebola to HIV to poxviruses and rhabdoviruses – almost any virus with a lipid envelope\textsuperscript{Lxiv}. We’ve suggested above that Progenitor and the T-Virus have such envelopes.

LJ-001 is able to inhibit viral entry into a cell, but it does not block the virus from binding to the cell membrane. Furthermore, it does not prevent a virus from replicating once it gets into a cell. As we’ve mentioned, the Reagent Refinement File states that the AT1521 reagent does not actually remove the virus from an infected individual, but slows its development. The properties of AT1521 sound a bit like those of LJ-001 to us.

There is a third possible explanation for the function of AT-1521, but it depends on the T-Virus sharing certain characteristics with certain other retroviruses – particularly HIV. A cellular protein called BST-2 inhibits the formation of the viral envelope, preventing enveloped viruses from escaping the cell. We have already speculated that the T-Virus is an enveloped virus, making BST-2 a good candidate for a therapeutic agent. It was recently revealed that BST-2 also has the ability to prevent certain immature HIV proteins from cleaving into their mature forms, preventing the virus from maturing and going on to infect new cells\textsuperscript{Lxv}. If the T-Virus also possesses an analog of the p40Gag protein, then BST-2 would affect it in a similar way. A reagent designed to fight the T-Virus might use liposomes containing stabilized BST-2 mRNA to get infected cells rapidly synthesizing large amounts of BST-2.

The Outbreak games also feature antiviral pills. Given their prevalence, we suspect these pills are nothing more than common antiviral drugs; if they were developed by Umbrella, then their completely legal pharmaceutical division was responsible. Numerous real-world antiviral drugs exist, tailored for everything from influenza to herpes to HIV. Since these antivirals seem to work on the T-Virus, which we believe is a retrovirus, it’s possible that these drugs – or at least the more effective “large” antiviral pills – were developed to fight HIV. HIV drugs are unlikely to be scattered all over the city, but it’s possible that doctors at Raccoon Hospital started distributing them once they realized that they were dealing with a massive retrovirus outbreak.

The final vaccine was developed as late as 2005 by WilPharma in the CG movie Degeneration. We don’t know anything about it, but we can propose that it is probably an actual vaccine, since no one is shown contracting the T-Virus and then getting cured afterward. The National Guardsmen sent to restore order in

The AT1521 reagent. Source: Outbreak: File #2
Harvardville are inoculated with the vaccine before they enter the quarantined zone, so that if they are exposed to the virus, the infection never takes hold. That is how a normal vaccine works. However, a person given a normal vaccine does not actually develop full immunity until about 14 days after he or she is inoculated. The WilPharma vaccine may have been augmented with anything from antibodies and adjuvants to antiretroviral drugs as a means to combat infection before the subject develops active immunity.

References

You didn’t think we were making this stuff up, did you?

Okay we kind of were.


Congratulations, you found the hidden message.


Thanks to Project Umbrella for hosting this report; additional thanks for images to the Let’s Play Archive, and to www.the-last-escape.biohazardfrance.com; and a very special thanks to Google, Wikipedia, and PubMed.
Birkin: It just doesn't make sense...

Don’t blame us. We did the best we could.