The *undead* in culture and science

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ABSTRACT

The *undead* have a significant role in mythology, religion, folklore, and literature. In the 1800s, the word *zombie* was used to describe reanimated corpses in the Caribbean who often worked on plantations doing long, arduous field work. The movie *White Zombie* was released in 1932 and exploited this folklore, but it ignored the fact that zombies represent one outcome in Vodou religious beliefs regarding death and the migration of spirits following death. The interest in zombies eventually led to sociological and medical investigations into zombification. Wade Davis reported that powders used by malevolent priests (*bokors*) contained tetrodotoxin, which could cause the neurologic changes underlying the zombie phenotype. Recent clinical studies have indicated that synthetic cannabinoids and synthetic cathinones can cause bizarre zombie-like behavior. According to Haitian folklore, zombies can develop when *bokors* reanimate someone who suddenly died from an acute illness or who was purposely poisoned. Recent studies in molecular biology suggest that the sequence of programmed cell death can be reversed when the stressor is removed and that cells, tissues, and bodies (at least in *Drosophila* flies) can recover. These scientific studies would support the remote possibility that the near dead might recover under certain circumstances but have residual neuropsychological dysfunction. Alternatively, the *bokors* could maintain control of their victims using drugs with properties similar to those of synthetic cannabinoids. The concept of zombification needs to be considered in the context of culture, religion, and science.

KEYWORDS Anastasis; synthetic cannabinoids; tetrodotoxin; Vodou; zombie

The recent death of filmmaker George Romero (1940–2017) invites us to revisit the cultural background of the living dead; that is, the undead, or zombies. The English word *zombie* (Haitian French: *zombi*; Haitian Creole: *zonbi*) was first recorded in 1819.¹ It represents an undead person who was created through the reanimation of a corpse, usually through magic or witchcraft. These individuals were often depicted as automatons without speech. The word most likely originated in West Africa and represents an important element in folklore in rural Haiti. Zombies represent one possible outcome in Vodou religious beliefs regarding death and the migration of spirits following death. Vodou practitioners recognize a supreme creator (*Bondye*) and multiple spirits (*loa*) who control particular aspects of life. However, books and films have exploited the idea of zombies and have significantly denigrated these cultural beliefs. As a result, most people are familiar with the ghoulish figures that threaten townsfolk, but many are unfamiliar with the cultural traditions that underlie the nearly 5000-year history of the undead. In addition, recent scientific studies have identified synthetic drugs that can

create the zombie phenotype and molecular events that can explain the reversal of death. In this review, we consider the undead in culture and literature, in movies, and in Haitian folklore and religion and review the limited medical studies on zombies, drugs that can create a zombie phenotype, and recent laboratory studies potentially relevant to reanimation.

THE UNDEAD IN LITERATURE

The zombie in literature involves two diametrically opposed stories. In some situations, the zombie is used to cause harm or to create profit for its creator; in other situations, the undead become completely whole and eventually join their maker in heaven. The earliest reference to the undead in literature appears in the Sumerian epic poem *Gilgamesh*, composed ca. 2700–2500 BCE. Gilgamesh, king of Uruk, and his companion Enkidu have just killed Humbaba, whose “shout is the storm-flood, his mouth, fire, his breath is death.”² Impressed with his prowess and beauty, the goddess Ishtar entices Gilgamesh, who rebuffs her. Enraged at this insult, Ishtar commands her father Anu to release the Bull of Heaven against

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Figure 1. Portions of Tablet V of the Epic of Gilgamesh. This cuneiform writing depicts Gilgamesh and Enkidu meeting Humbaba, guardian of the Cedar Forest. The tablet dates to the Old Babylonian Period, 2003–1595 BCE. Photograph by Osama Shukir Muhammed Amin, FRCP; Wikimedia, open access.

Gilgamesh and Enkidu, vowing to reanimate the dead if he refuses (*Figure 1*).

Father, make the Bull of Heaven. Let him kill Gilgamesh in the very place he lives;
let the bull glut himself on Gilgamesh.
If you do not give me the bull,
I will smash in the gates of the netherworld;
I will set up the [ruler] of the great below,
and I will make the dead rise, and they will devour the living,
and the dead will increase beyond the number of the living.²

Though Ishtar's undead were intended to cause harm to the living, reanimation of the dead in the Bible serves another purpose. The miraculous resurrection of Lazarus prepares the faithful for the resurrection of Jesus. In John 11:43–45, Jesus raises Lazarus from his tomb:

And when he thus had spoken, he cried with a loud voice, "Lazarus, come forth." And he that was dead came forth, bound hand and foot with graveclothes: and his face was bound about with a napkin. Jesus saith unto them, "Loose him and let him go." Then many of the Jews which came to Mary, and had seen the things which Jesus did, believed on him.

The reanimated Lazarus continues to life, apparently no worse for having been dead for 4 days.

Then Jesus six days before the Passover came to Bethany, where Lazarus was which had been dead, whom he had raised from the dead. There they made him a supper. Martha served: but Lazarus was one of them that sat at the table with him. (John 12:1–2)

Although Lazarus is not mentioned again in the Bible, some religions maintain that he ultimately became a priest and lived for 30 more years.³

The undead in medieval literature appear as links to pestilence and plague or as "mirrors of the living," allowing the living to interpret messages from beyond the grave. In *Sir Gawain and the Green Knight*, for example, the knight is beheaded but does not die. The presence of this "undead" knight throughout the tale serves "as a representation of death

to Gawain—a reminder . . . that Gawain must not only live with honor but die with it also."⁴

By the 19th century, the undead in literature are primarily vengeful creatures. The vampires in Bram Stoker's *Dracula* feed on the living to satisfy their hunger and to perpetuate the species. Mary Shelley's *Frankenstein* depicts a corpse reanimated by electricity that turns on its creator. Vampires and zombies appear throughout the literature in the 20th century; authors varying from T. S. Eliot to Truman Capote to Richard Matheson have used the "Lazarus effect" in their poems, short stories, and novels. A modern twist in literature is to introduce the undead into classic literature; for example, *Pride and Prejudice and Zombies*, in which Elizabeth Bennet and her sisters fight the marauding undead.⁵

Though older literature often uses natural events as the reanimating force, new literature tends to attribute zombification to "medicine gone bad." Published in 2010, the novel *Feed* postulates that a virus used to cure cancer and another virus used to cure the common cold combine in mammalian hosts to create a disaster.⁶ The hybrid virus disrupts cellular events to transform living humans into creatures with the zombie phenotype.

ZOMBIES IN CINEMA

Released in 1932, the first feature-length zombie film, *White Zombie*, starred Bela Lugosi, who played a plantation owner in Haiti whose sugarcane fields were worked by zombies (*Figure 2*). The United States occupied Haiti from 1915 to 1934, and this film reflected the social structure of the time. The occupation emphasized the class differences among the white and mulatto elite and the black workers. In his article on *White Zombie*, Tony Williams pointed out that "black zombie

Figure 2. A zombie at twilight in a field of sugarcane in Haiti. By Jean-Noel Lafargue; Wikimedia, Open Access.

slavery in the film thus represents a macabre version of the forced labor system which the US inflicted on the Haitian population in 1918.⁷ Negatively reviewed at the time due primarily to the poor acting, the film nevertheless was financially successful.⁸ Lugosi again portrayed a zombie slave owner in his 1942 film, *Bowery at Midnight*. The hapless people who come to his soup kitchen wound up as zombies in the basement.⁹

A few horror movies in subsequent decades focused on zombies, but the genre became popular with George Romero's zombie series, the first to portray them as cannibalistic. The first in the series, *Night of the Living Dead*, was released in 1968 and featured several people trapped in a farmhouse beset by human-like creatures contaminated by radiation who "keep coming back in a bloodthirsty lust for human flesh!"¹⁰ Romero's sequels, *Dawn of the Dead* in 1978 and *Day of the Dead* in 1985, proved that the lust for zombie movies was alive and well. *Diary of the Dead* in 2008 was the fourth, and last, sequel. Director Sam Raimi's successful *Evil Dead* series spawned comic books, films, a television series, a musical, and video games.¹¹

Zombie films are not always horror movies. *Shaun of the Dead*, for example, stars British comedians Simon Pegg and Nick Frost trying to survive a "zombie apocalypse" as they lurch from one crisis to the next.¹² Sam Raimi's *Evil Dead* third sequel *Army of Darkness* has many comedic moments, culminating in its iconic line, "Ash. Housewares," as Bruce Campbell's character blasts a zombie in S-Mart.¹³

The British television series *Doctor Who* reanimates the dead in the 2014 episodes "Dark Water" and "Death in Heaven," turning occupants of cemeteries into world-conquering Cybermen, recalling Ishtar's threat to reanimate the dead "to devour the living" in *Gilgamesh*, composed over 4000 years earlier.^{2,14} The current TV series *The Walking Dead* traces zombification to a "solanum" virus that lies dormant in every human's brain. Upon death, it may reactivate, causing reanimation. This virus begs the question: Who actually are the walking dead—the zombies or the exhausted survivors?¹⁵

ZOMBIES IN HAITI: A FOLKLORE INTERTWINED WITH VODOU

Haitians participate in multiple religions, including Roman Catholicism (the majority) and Protestant denominations.¹⁶ The number participating in Vodou is uncertain and is likely underestimated by surveys. Vodou (meaning spirit/deity in the Fon language) became an officially recognized church in 2001 with the establishment of the Eglise Voudou d'Ayiti (the Vodou Church of Haiti). Vodou practitioners recognize a supreme creator (*Bondye, Bon Dieu*) and multiple spirits (*loa*) who control particular aspects of life, such as Kouzin Zaka (the spirit of agriculture). Haitian Vodou incorporates elements of African Vodou, Roman Catholicism, and mysticism. Vodouists recognize everything as spirit, both seen and unseen, the latter including ancestors and recently deceased people, and they serve these spirits through an oral tradition that offers prayers and devotional rites. Vodouists revere death and consider it a great transition to an afterlife. Some practitioners believe that the person's spirit (*ti bon ange*, little good angel) leaves the body, hovers

above the body for 7 days, and then descends into dark waters or other locations for 1 year and 1 day. After this time, the community celebrates the death; the *ti bon ange* is reclaimed, placed in a jar, and then taken to the forest to wait for rebirth. This belief that the deceased spirit exists for a year and a day following death provides an intersection with the rural Haitian folklore regarding zombies. The *bokor* or sorcerer can capture the spirit of the dead and sell it as good luck to other people. In some situations, the *bokor* can reanimate the corpse into a zombie who works as a slave, usually in agricultural fields. Each year in Haiti multiple zombies are reported.

NEUROLOGY: CLINICAL STUDIES

Littlewood and Douyon reported three cases of zombification in Haiti in 1997 in *The Lancet*.¹⁷ The first case was a 30-year-old woman who died following a short febrile illness. Three years following her death, she was recognized by a friend wandering near the village. Her parents accused her husband of zombifying her following an affair. She was thin, walked extremely slowly and stiffly, would occasionally murmur a few incomprehensible words to answer questions, and required assistance to feed herself. Her electroencephalogram was within normal limits. The presumptive diagnosis was catatonic schizophrenia. The second case was a 26-year-old man. He died at age 18 following an acute febrile illness. Nineteen months after his death, he reappeared at a local event. His parents accused his uncle of zombifying him. However, the uncle claimed that this was a trick by the man's father. The patient spent most of his day in characteristic posture; when he did walk, the posture and gait appeared to be normal and steady but slow. His neurologic examination was within normal limits. He had no thought disorder, hallucinations, or catatonia. The presumptive diagnosis was organic brain syndrome and epilepsy consistent with a period of anoxia. The third patient was a 31-year-old woman who died following an acute febrile illness and then reappeared 13 years after her death. Her neurologic and mental status examinations were within normal limits. Her speech was limited but appropriate with short sentences, possibly secondary to low intelligence. The presumptive diagnosis was a learning disability. The authors assume that this case was explained by mistaken identity. Computed tomography scans of the second and third cases were within normal limits. Littlewood and Douyon suggested that bereaved families mistakenly identify wandering mentally ill strangers with zombie features as their departed relative.¹⁷ Overall, the limited information in these case studies does not provide a comprehensive definition of the neurological or psychological changes in individuals with a zombie phenotype.

Two neuroscientists have studied the behavior of zombies and developed a comprehensive but speculative model for alterations in the zombie brain that underlie their behavior.¹⁸ Zombies have an impulsive reactive aggression disorder caused by loss of orbitofrontal control of the amygdala. Ataxia is caused by disease in the cerebellum. Hippocampal damage causes problems with long-term memory consolidation. The

language circuit is destroyed and explains the aphasia. Their reduced pain responses are secondary to damage in the somatosensory cortex. Degeneration in the posterior parietal cortices causes an attention locking disorder. Dysfunction in the ventral striatal reward pathways leads to addictive behaviors, such as flesh addiction. A zombie outbreak in Brooklyn in 2016 suggested that a single drug can cause this phenotype through diverse effects in the central nervous system (see below).

DRUGS AND VIRUSES AS POTENTIAL EXPLANATIONS FOR THE CREATION OF ZOMBIES

Tetrodotoxin

Wade Davis studied the cultural beliefs and potential explanations for zombies in Haiti in 1982 and published a paper entitled “The Ethnobiology of the Haitian Zombie” in the *Journal of Ethnopharmacology* in 1983.¹⁹ This paper provides a good discussion of the complex belief systems in Vodou related to the migration of spirits following death. Davis claimed that malevolent priests (*bokors*) could create zombies by poisoning their victims, reviving them through magical processes preferably after burial, and then controlling them through the use of psychoactive medications.¹⁹ He collected various powders provided by *bokors* and claimed that the principal compound causing the zombie state was tetrodotoxin, a potent frequently fatal neurotoxin found in puffer fish. This toxin can be absorbed by ingestion, injection, or inhalation or through breaks in the skin. It blocks fast voltage-gated sodium channels and causes muscle paralysis, including respiratory arrest. Clearly the use of powders containing this toxin requires special skills and/or luck. However, the claims by Wade Davis were subsequently discounted by pharmacologists in Japan who could not identify any active toxin in these powders; the claims were critically analyzed by William Anderson, who noted that the science underlying the Davis claims was relatively poor and that there were important ethical concerns regarding this work, including the possibility that he tried to pay a *bokor* to create a zombie.^{20,21}

Synthetic marijuana

Adams et al. reported a zombie outbreak caused by synthetic cannabinoids in New York.²² The media reported 33 people with “zombielike” behavior in Brooklyn in July 2016. Eighteen of these patients were transferred to emergency centers; serum, whole blood, and urine samples were obtained from eight of them. The index patient was a 28-year-old man who responded slowly to questions and had a “blank stare.” Physical examination revealed lethargy, a Glasgow Coma Scale score of 13, and intermittent periods of groaning and slow mechanical movements of his arms and legs. His behavior normalized after approximately 9 hours of observation. Laboratory tests and drug screens did not reveal any alternative explanations for this behavior. All eight patients had AMB-FUBINACA acid metabolites in their serum. AMB-FUBINACA is an indazole-based synthetic cannabinoid (formula $C_{21}H_{22}FN_3O_3$), an extremely potent synthetic cannabinoid present in AK-47 24 Karat Gold. These drugs are direct cannabinoid 1 receptor agonists.

Flakka

Other synthetic drugs can create bizarre behavior, including agitated delirium, violent outbursts, and confusion. Flakka (alpha pyrrolidinovalerophenone, alpha-PVP, formula $C_{15}H_{21}NO$) is a synthetic cathinone that stimulates the release of dopamine and inhibits the reuptake of epinephrine, norepinephrine, and serotonin in the central nervous system.²³ Crespi reported a 17-year-old student who developed an altered mental status with agitation and psychotic behavior following one ingestion of flakka.²⁴ This patient required symptomatic treatment with benzodiazepines and antipsychotics for days before she became somewhat coherent. However, following improvement, she continued to have residual symptoms with agitation and reduced cognition. There are reports of epidemic use of flakka in Florida.²⁵

Viruses

Mosquitos carry the Zika, dengue, chikungunya, and West Nile viruses and can create epidemics of mosquito-borne infections. Roth et al. reported 28 documented outbreaks of dengue, chikungunya, and Zika in the Pacific region between 2012 and 2014, which involved at least 120,000 people.²⁶ The Zika virus spread rapidly throughout South America and North America in 2015 and 2016.²⁷ This virus can cause fetal microcephaly and neurological syndromes in adults, including Guillain-Barré syndrome and encephalitis.²⁸ Mutations in this virus could change its neuroinvasive potential and create new syndromes, including chronic encephalopathy with features similar to the zombie phenotype. Annamalai et al. reported that isolates from the Western Hemisphere contained an N-linked glycosylated site in the viral envelope protein that increased neuroinvasion in a murine model.²⁹ Isolates from an African lineage did not have this site. This single mutation might explain the increased pathogenicity of Zika infections in the Western Hemisphere and provides scientific support for the idea that viral mutations can have profound consequences. The West Nile virus was initially isolated in the United States in 2009. This virus can cause neuroinvasive disease, including encephalitis, meningitis, and poliomyelitis, and up to 50% of patients with encephalitis have important neurological sequelae after recovery.³⁰ Changes in the mosquito populations, host populations, and viral virulence (including neuroinvasion) and geographical spread into naïve populations could create complex interactions that could cause epidemics of viral infection and large numbers of survivors with physical and mental impairment, including the zombie phenotype.^{31,32}

SCIENTIFIC INVESTIGATIONS INTO THE REVERSAL OF DEATH

Programmed cell death or apoptosis eliminates abnormal or injured cells and prevents injury to adjacent healthy cells in various disease states. This process is thought to be irreversible after mitochondrial fragmentation and caspase activation occurs. Damaged mitochondria release several factors, including cytochrome C, which activate the protease caspase that then destroys structural and functional components in the cell. Morphologic changes include nuclear condensation, cell shrinkage, and membrane blebbing (*Figure 3*).³³ Tang and coworkers have recently reported the reversal of late-stage apoptosis in multiple cell

Figure 3. Morphological changes during apoptosis. **(a)** Electromicrograph of untreated human cervical cancer cells (HeLa) demonstrates the normal structure of HeLa cancer cell. Nucleus (N), nucleolus (NL), and the cytoplasm appeared without abnormal changes ($\times 4600$). **(b)** Zerumbone (ZER)-treated (24 hours) human cervical cancer cells (HeLa) demonstrate morphological features of early apoptosis: cell shrinkage, chromatin condensation (arrow), and integrity of plasma membrane ($\times 6000$). **(c)** ZER-treated human cervical cancer cells (HeLa) demonstrate the condensed cristae of mitochondria (MC) as a typical morphological feature in apoptosis (arrow) ($\times 27,500$). **(d)** ZER-treated (48 hours) human cervical cancer cell line (HeLa) demonstrates morphological features of intermediate apoptosis: cell shrinkage, chromatin condensation (white arrow), and membrane blebbing (small white arrow) ($\times 6000$). **(e)** ZER-treated (72 hours) cervical cancer cells (HeLa) demonstrate morphological feature of late apoptosis: nuclear collapse, continuing blebbing, and apoptotic body formation (arrow) ($\times 10,000$). Reprinted from Abdel Wahab et al³³; Open Access.

lines.³⁴ They exposed tissue culture cells to apoptosis inducers and allowed the cells to develop multiple morphologic and biochemical changes consistent with apoptosis. However, when the inducer was removed, the vast majority of the cells underwent reversal of apoptosis and recovered. However, some of the recovered cells developed permanent genetic changes. These investigators also studied the reversal of apoptosis in vivo using *Drosophila* flies exposed either to a cold stress or to a protein starvation stress.³⁵ The programmed cell death sequence pathway was activated in these flies, but when the stress was removed the flies recovered. In addition, these flies produced new healthy progeny. This process is called *anastasis* (from the Greek *ἀνάστασις*, rebirth) and indicates that the molecular events associated with cell death are much more complicated than a simple unidirectional process.

SUMMARY

Many Haitians consider zombification real and verifiable. There are estimates of up to 1000 new cases per year. The

sequence of events could involve near death with recovery or poisoning with reversal or recovery. A typical sequence involves a young person suddenly becoming ill, possibly through poisoning or sorcery, considered dead by his or her family, placed in a tomb, stolen by a *bokor* within the next few days, and subsequently returned to life and activity but without full awareness and neurofunction. The zombie becomes a slave of the *bokor* and works secretly on his land. Local beliefs consider the physical body separate from the animating spirits and the mind, and in some cases the *bokor* captures the spirit of the dead. These beliefs help communities cope with events that are beyond their control or beyond their understanding. Medical explanations for zombification include catalepsy and other psychiatric disorders, residual effects from neurotoxins, drug toxicity, near death in a location with limited medical care, and a mistaken belief of death. The process of anastasis suggests that cells, tissues, and potentially bodies can progress through programmed cell death and then recover if the initial stress stops. It would not be difficult to imagine that the

recovery process is incomplete, with the potential for persistent organ dysfunction, including the central nervous system. This outcome (i.e., reanimation) would clearly enhance the *bokor's* power and standing in the community and provides an explanation or psychological cushion for unusual, unexplained events in the community. Synthetic cannabinoids can have profound effects on neuropsychological functions, and these and other drugs or herbal preparations provide a potential explanation for zombie-like behavior. The concept of zombification needs to be considered in the context of culture, religion, and science.

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