Management of Cough

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ABSTRACT

Cough is the most frequent symptom for which patients consult with their health care provider throughout the world. This symptom could be happened not only in sick individuals but also healthy individuals. At some stage, it is distressing, inhibits normal social activities, and reduces quality of life. Besides these detrimental effects, cough is the most effective defense mechanism to eliminate foreign materials, including various pathogens, from the respiratory tract. It begins with a series of breathing maneuvers which triggers sudden expulsion of air which is divided into three phases, i.e., inspiration, compression, and expiration phase. Cough occurs due to activation of mechanical or chemical sensory receptors in the larynx and lower respiratory tract which stimulates reflex arc complex. This stimulus is then transmitted to the afferent pathway to the cough center in the medulla through the vagus nerve to trigger expiration muscles to produce cough. It is important to know the cause of cough because cough is an indicator for patients and doctors for early diagnosis and therapy of disease. Therefore, cough is classified into acute, subacute, and chronic according to its duration. Available medications for symptomatic management of cough are inadequate due to lack of proven efficacy and/or their undesirable or intolerable side effects. This article aims to provide information on cough management to improve therapeutic effectiveness and patient quality of life.

BACKGROUND

Cough is the most effective defense mechanism to eliminate foreign materials, including various pathogens from the respiratory tract.1,2 This symptom not only affects sick individuals but also healthy individuals. An excessive and persistent cough can be associated with non-malignant chronic disease, with or without excessive mucus production. A persistent cough is hazardous to the patients due to its effect on breathing, social activity, and sleeping. Other than that, it can reduce the quality of life and cause embarrassment while socializing, and cause syncope, urine incontinence, muscle pain, insomnia, and fatigue.3

A population study showed that the prevalence of cough varied between 3% and 40%.1 An epidemiological survey revealed that 11-18% of the general population reported persistent cough. Although it was not known whether the cough was normal or associated with a disease. This report could be caused by smoking, exposure to urban population or irritants in a closed or opened environment, air pollution, or undiagnosed cough-related disease. Around 10-38% of patients with persistent cough were outpatients in specialist practices in the United States.2

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There are many over-the-counter drugs. However, usage is recommended based on habit and traditional practice. The use of these drugs is not supported by clinical studies regarding drug quality that fulfilled the evidence-based modern medicine standard. An internet survey on 1,120 participants from 29 countries in Europe proposed that the effectivity of cough medicine is limited, thus cough therapy is deemed unsatisfactory. Therefore, an understanding of the pathophysiology of cough related to an underlying disease is needed to obtain appropriate and directed management of cough.

This article discussed (i) definition, (ii) pathophysiology, (iii) classification, and (iv) treatment of cough.

Definition

A cough is not always an abnormal clinical symptom. It is an explosive expiration to defend the lungs by increasing secretion and particle cleansing from the respiratory tract. Cough is needed to clean the respiratory tract from mucus and secretions (approximately 20-30 ml per day) and the amount of respiratory secretion depends on daily exposure to irritants. It also protects the respiratory tract from aspiration of foreign materials occurred due to aspiration or inhalation of certain particles, pathogens, liquid accumulation, postnasal drip, inflammation, and mediators related to inflammation.

Cough is started with a series of respiratory maneuvers which triggers sudden expulsion from the air, creating a characteristic cough sound. The mechanical process of cough is divided into three phases:

1. Inspiration phase: gas inhalation can be at least 50% of tidal volume or as much as 50% of vital capacity needed for an effective cough.
2. Compression phase: glottic closure maintains intrathoracic pressures combined with contraction of chest wall muscles, diaphragm, and abdominal wall.
3. Expiration phase: glottis is opened, producing expiration airflow and high cough sound and compression on the large respiratory tract. High airflow excretes mucus and cleansed the respiratory tract.

The coughing sound produced during the first three phases is caused by an explosion heard during the expulsion phase. This sound is composed of noise waves. This phase is accompanied by an intermediate phase which occurs when airflow decreases due to sound amplitudes. Finally, the third phase occurs, which is known as the sound or glottis phase. It is produced by vibration from a half-closed glottis, which resulted in periodic and regular noise.

Pathophysiology

Stimulation of the reflex arc complex results in coughing that begins with an irritation to cough receptors in the trachea, carina, large respiratory tract branch, small respiratory tract, and the pharynx. Mechanical and chemical stimuli are responded by cough receptors in the larynx and tracheobronchial. Chemical receptors are sensitive to acid, heat, and capsaicin-like compound, which triggers cough reflex through type 1 vanilloid activation (capsaicin receptor). These receptors can also be found in the external auditory canal, eardrum, paranasal sinus, pharynx, diaphragm, pleura, pericardium, and the abdomen. These receptors only respond to mechanical stimuli, i.e. to touch or movement.
Figure 2. The pathophysiology of cough reflex and targets for antitussive agents. Pro-tussive stimuli activate the sensory nerve fibers in the airway and travel through the vagus nerve to the medulla which then ends at the nucleus tractus solitarius (NTS). The respiratory pattern generator receives message from the second-order neurons, which modifies the activity of the inspiratory and expiratory motoneurons leading to cough. Antitussives work peripherally or centrally in pre- and post-synapses.
The cough reflex arc complex consists of:

1. Afferent pathway: sensory nerve fibers (vagus nerve branches) located in ciliary epithelia from the upper respiratory tract (pulmonary, auricular, pharynx, superior larynx, and gastric) and branches of the heart and esophagus from the diaphragm. This afferent impulse is directed diffusely to the medulla.

2. Central pathway (cough center): central coordination area located in the upper part of the brain stem and the pons.

3. Efferent pathway: impulses from the cough center are directed through the vagus, phrenic, and motoric nerves of the spine to the diaphragm and abdominal walls and muscles. Retroambigous nucleus, derived from the phrenic nerve and other spinal motoric nerves, send impulses to inspiration and expiration muscles, and ambiguous nucleus, through the laryngeal branch of the vagus nerve to the larynx. Mucosa and upper respiratory walls (from upper respiratory tract to terminal bronchioles and lung parenchyma) are the final of the afferent pathway of the vagus nerve.

Cough reflex begins with a stimulus to cough receptors. Stimulus from the afferent pathway of sensory nerve fibers is divided into three main groups: Ad-fibers or rapidly adapting receptors (RARs), C-fibers, and slowly adapting stretch receptors (SARs). These nerve fibers are differentiated by their neurochemical property, anatomic location, conduction speed, physiochemical sensitivity, and adaptation to lung inflation. This stimulus is then transmitted to the afferent pathway through the vagus nerve to the cough center in the medulla, under control of a higher cortex center. The cough center produces efferent signal transmitted to the vagus nerve, phrenic nerve, and spinal motoric nerves to trigger expiration muscles to produce cough.

The sensory nerve fibers acting in cough reflex are explained further below:

1. Ad-fibers or rapidly adapting receptors (RARs)
   RARs are myelinated nerve fibers with ends approximately inside or slightly under the intrapulmonary respiratory tract epithelia and respond to mechanical changes in the respiratory tract during normal breathing condition. These fibers respond most to cough stimulus and hold important roles in cough reflex. RARs are differentiated from other respiratory tract afferent nerve fibers because of their adaptation speed (1-2 seconds) in advanced lung inflation. Other distinguishing properties include the sensitivity of RARs to lung collapse or deflation, responsivity of RARs to dynamic changes from lung compliance, and conduction speed (4 to 18 meters/second) to maintain continuous lung inflation. Mechanical stimuli such as mucus secretion or edema increase RARs activity more than chemical stimuli such as bradykinin and capsaicin.

2. C-fibers
   Non-myelinated C-fibers are the main afferent nerve fibers innervating the respiratory tract and lungs. The conduction speed of C-fibers is < 2 meters/second. This nerve fiber is different from RARs and SARs because of insensitivity to mechanical stimulus and lung inflation. Citric acid, bradykinin, and capsaicin are stimulants of C-fibers that induce cough. These stimulants act directly to C-fibers, not through the effect on the respiratory tract smooth muscles. E2 prostaglandin, adrenalin, and adenosine sensitize C-fibers through the direct effect of bradykinin and capsaicin to the peripheral nerve end.

3. Slowly adapting stretch receptors (SARs)
   SARs are afferent fibers thought to be involved in the Hering-Breuer reflex, which ends inspiration and starts expiration when the lungs are inflated sufficiently. The activity of SARs does not change upon cough-causing stimulus and SARs is indirectly involved with cough reflex. SARs are highly sensitive to mechanical stimuli occurring in the lungs during breathing. The activity of SARs increases during inspiration and reaches its peak at the beginning of expiration. SARs can be differentiated from RARs based on their conduction potential activity speed and lack of adaptation to lung inflation. SARs are also differently distributed in the respiratory tract and mostly found at the end of the intrapulmonary respiratory tract. The activity of SARs causes central inhibition from breathing and cholinergic inhibition in the respiratory tract decreases phrenic nerve activity and smooth muscle tone of the respiratory tract.

Classification
Cough is one of the signs of respiratory and pulmonary disease. It can be an important indicator for patients and doctors for early diagnosis and therapy of disease. The American College of Chest Physicians (CHEST) in 2006 published a guideline on coughing. The guideline classified cough into three groups, i.e. acute, subacute, and chronic. This classification is thought to be useful for diagnosis and therapy of cough.
It is widely used throughout the world. Below is a further explanation on cough according to the CHEST classification revised in 2017.11

1. Acute cough

Acute cough refers to a cough occurring for a maximum of 3 weeks. It is usually caused by infection to the upper respiratory tract, acute bronchitis, or tracheobronchitis due to bacteria, or more often due to virus. Patients with upper respiratory tract infections rarely seek medical treatment. Acute cough caused by an infection usually resolves itself and the patients usually recover within one or two weeks along with infection cleansing.5

2. Subacute cough

Subacute cough is defined as a cough occurring within 3-8 weeks. Increased bronchial hyperresponsivity can be permanent due to specific infection (e.g. M. pneumoniae) which causes a discomforting subacute cough for several weeks even though the underlying infection had subsided. Hypersensitivity of the respiratory tract after infection which causes subacute cough is rarely investigated.5

Continuous cough despite resolved infection can also be caused by B. pertussis. Regardless of children and adult previous vaccination history, we need to eliminate pertussis infection. Cough caused by B. pertussis is generally induced by paroxysmal cough episodes with a characteristic of whooping inspiration, especially in children. This symptom is not found in adults.5

Figure 3. Acute cough algorithm for the management of adult patients with cough lasting <3 weeks. Do not forget to screen for the red flags as potential life-threatening condition. In endemic areas or high-risk populations, consider the presence of TB. Routinely assess cough severity or quality of life of the patient before and after treatment. Follow patients 4-6 weeks after initial visit.11
Figure 4. Subacute cough algorithm for the management of adult patients with cough lasting 3 to 8 weeks. Do not forget to screen for the red flags as potential life-threatening condition. In endemic areas or high-risk populations, consider the presence of TB. Routinely assess cough severity or quality of life of the patient before and after treatment. Follow patients 4-6 weeks after initial visit.\textsuperscript{11}

The etiologies of non-infectious subacute cough include gastroesophageal reflux, aspiration, and bronchial asthma (can be a diagnosis if accompanied by skin sensitization by seasonal allergens or symptoms start to occur after exposure of allergen from the environment or pollutant).\textsuperscript{5} Gastroesophageal reflux can be caused by cough mechanism due to esophagus-vagal stimulus, esophageal-bronchial reflex or regurgitation, with or without aspiration.\textsuperscript{12} During the excessive fluid period such as pulmonary edema, subclinical congestive heart failure can be a cause of acute and subacute cough. A rare subacute cough case is pulmonary sequestration in Tourette syndrome which manifests as a cough with paroxysmal episode.\textsuperscript{5}
3. Chronic and persistent cough

Persistent cough for more than 8 weeks is defined as chronic cough. The cause of acute and chronic cough is important because their epidemiology and etiology are different. Chronic cough is a common complaint that is often found in primary and secondary health services. Chronic cough causes a considerable epidemiological burden and affects almost 10% of all adult population. Chronic cough is also a significant clinical problem, causing the decreased quality of life which is challenging for clinicians.13

R. S. Irwin in 1977 analyzed and stated that a number of diseases or conditions that cause chronic or persistent coughing are caused by small anatomical locations of cough afferent receptors. Smoking and the use of ACE-inhibitors are only a small part of the cause of chronic cough. There are three dominant etiologies in most patients that can explain chronic cough: upper respiratory tract cough syndrome attributed to various conditions of the nose and sinus, previously known as postnasal drip (PND) syndrome, asthma, and gastroesophageal reflux disease (GERD).5,12 These three diagnoses were found in 92-100% of non-smoking patients, not using ACE-inhibitors, and had normal thorax radiographs. Upper respiratory tract cough syndrome, asthma, non-asthmatic eosinophilic bronchitis, and GERD are still the most frequent causes in developing regions in the world (where TB is considered as the cause of chronic cough in endemic areas).5

Boulet, et al. in 1994 compared the inflammatory degree of respiratory tracts on the biopsy tissues of bronchus and bronchoalveolar lavage fluid (BALF) between non-asthmatic chronic cough and control to investigate the pathology of the chronic respiratory tract. Samples from cough patients had relatively higher inflammatory cells than control (especially mononuclear cells) and showed epithelial desquamation, submucosal fibrosis, inflammation of the mitochondria, dilatation of smooth endoplasmic reticulum, and increased activity of nucleus metabolism. There was no insignificant differences compared to the etiology of chronic cough (PND and GERD). Mast cells are found in the BALF of non-asthmatic cough patients compared to control. A recent study by Niimi, et al. also found that mast cell hyperplasia is a characteristic in non-asthmatic chronic cough patients.13

Chung and Pavord classified chronic cough into eosinophilic respiratory tract disease responsive to corticosteroids, such as bronchial asthma, cough variant asthma (CVA), eosinophilic bronchitis, and steroid-resistant disorders such as PND and postnasal drip (PND) or rhinosinusitis. Cough is reduced partly or thoroughly in 59% of patients with β agonist inhalation followed by inhaled corticosteroid (ICS). CVA is the most frequent cause of chronic cough, which can be reduced by bronchodilator administration. Patients coughing due to GERD experienced worsening cough sound, increased cough (90%), increased appetite (87%), and throat cleansing (74%).13,14 Excessive remodeling of the respiratory tract in bronchial asthma and CVA causes deformation of the respiratory tract during bronchoconstriction, causing chronic cough.13

Further study on phase I-II from European Community Respiratory Health Survey (ECHRS) revealed that chronic cough/phlegm is a strong marker for individuals with moderate/severe asthma.13 Almost 30% of CVA is reported to develop into bronchial asthma and showed that several types of CVA can be predecessors to bronchial asthma. Few types of PNS syndromes, such as allergic rhinitis and atopic cough also respond to corticosteroid. However, their prognosis and impact on the quality of life are different from bronchial asthma and it is difficult to decide the duration of corticosteroid therapy. Therefore, it is important to differentiate cough responsive to corticosteroid from other types of cough.15

Other than various manifestations of chronic cough explained above, there is a new clinical concept of fungus-associated chronic cough (FACC) defined as a chronic cough related to basidiomycetes in induced sputum. FACC manifests in: (i) chronic cough, (ii) fungi found in sputum, especially basidiomycetes, and (iii) good clinical response to antifungal treatment. Previous studies detected basidiomycetes in 39 sputum samples (22.8%) from 171 chronic cough patients. There are three types of FACC: (i) single colonization of basidiomycetes (pure-FACC), (ii) sensitization of basidiomycetes (allergic fungal cough, AFC), and (iii) colonization and/or sensitization of basidiomycetes other than a chronic cough, such as CVA, atopic cough, upper respiratory cough syndrome, and hypersensitive cough syndrome.3,16
Figure 5. Chronic cough algorithm for the management of adult patients with cough lasting > 8 weeks. Do not forget to screen for the red flags as potential life-threatening condition. In endemic areas or high risk populations, consider the presence of TB. Routinely assess cough severity or quality of life of the patient before and after treatment. Follow patients 4-6 weeks after initial visit.11
Other chronic cough causes often found in children and occur without underlying medical disease or response to medical therapy are psychogenic cough, habit cough, or tic cough. Nevertheless, these disorders should be differentiated from other chronic coughs such as refractory chronic cough, upper respiratory cough syndrome, vocal cord dysfunction syndrome, and hypersensitive cough syndrome. To date, there is no guideline in differentiating these types of cough.17

Treatment

1. Pharmacology

Causal therapy should be preferred if feasible. If not, however, in cases such as in acute respiratory infection due to virus or only effective if postponed (such as in TB), symptomatic therapy can be considered along with therapy to causes underlying the cough.5

Central antitussive

a. Opioids, such as morphine and codeine, works centrally on the cough center. Opioid-type antitussive has side effects and a higher risk of addiction. Opioids are recommended as an effective symptomatic therapy in disturbing dry cough. It is less effective for cough caused by common cold.5,6,10

- Codeine is mostly used and often considered as a basic antitussive. It is activated by CYP2D6 into morphine, which then undergoes glucuronidation. The degree of metabolism may vary dramatically due to a significant genetic difference in cytochrome P450 which depends on the monooxygenase activity. A fast metabolizer patient changes most codeine into morphine through the liver, causing toxicity potential. Meanwhile, in slow metabolizer, only a few of the drugs are converted, reducing drug effectiveness.5,6,10

b. Non-opioid antitussive is preferable for acute cough due to lower potential of misuse and addiction than its opioid counterpart.5

- Dextromethorphan significantly suppresses acute cough. The effect is shown in the administration of a single 30 mg dose compared to placebo in six studies. Dextromethorphan has a relatively slow onset and reaches its peak after two hours of administration. Slow penetration through the blood-brain barrier and retention to the nerve system causes the longer working duration of this antitussive.4,6,10

- GABA (γ-aminobutyric acid) is an inhibitory neurotransmitter in the central nervous system also found in the lungs. According to Ryan, et al., Gabapentin produces a suppressive effect on cough reflex in the center.6,10

- Local anesthesia such as lidocaine, benzonatate, bupivacaine, and mexiletine has been investigated to suppress coughing. It is the most effective antitussive, but its use is still controversial and becomes the last resort in patients with irritative cough. Local anesthesia interrupts electrophysiological activity on cough receptors and afferent receptors (e.g. during bronchoscopy). Local administration reversibly inhibits the action potential of vagus-pulmonary afferent nerve. This activity is thought to be caused by inhibition to the voltage-gated sodium channel.6,10

- Diphenhydramine, a first-generation antihistamine H1, is approved in several countries (including England and the United States) as an over-the-counter (OTC) antitussive. It is reported to reduce cough reflex sensitivity in patients with cough due to URTI.4

- Butamirate is widely used in Europe as an OTC antitussive. A cross-over placebo-controlled study revealed that none of the 34 subjects who finished the study experienced significant improvement after the administration of butamirate.4

Peripheral Antitussive

- Levodropropizine is a non-opioid agent that works in the peripheral nervous system. This drug modulates sensory neuropeptides in the respiratory tract and is given orally. A clinical trial on adults in Indonesia indicated that levodropropizine had better antitussive effect compared to placebo and morclofone and was equal to cloperastine.5,6
Menthol is produced by *Mentha arvensis*. Menthol inhalation suppresses cough reflex and can be prescribed as crystal BPC or in a special capsule, although the suppressive property is brief.\(^4,7\)

Throat lozenges can also reduce cough and flu symptoms through relieving activity on the mucosal membrane. The effect of throat lozenges is widely discussed in the fifth American Cough Conference in 2015. Most delegates agreed on the effectiveness of throat lozenges, but no studies expressed the effect.\(^4,7\)

### Expectorant

Expectorant reduces irritation to cough receptors by increasing mucus accumulation through “coughing up”. It is the most frequently used drug for respiratory diseases in German (e.g. ambroxol and N-acetyl cysteine). In chronic obstructive pulmonary disease (COPD) and bronchiectasis cases, expectorant is recommended to relieve cough due to thick secretion production. Many patients reported the effectiveness of expectorant in acute bronchitis cases.\(^4\)

The following describes several examples of expectorant:

- Ambroxol, a bromhexine active metabolite, is the most popular medicine in German. It also shows other antitussive effects other than expectorant.
- Pholcodine and guaifenesin are also used as an expectorant.
- Ammonium chloride is an acid-producing salt that is considered to provide an expectorant effect in loosening phlegm.\(^4,6\)

### Mucolytic

Mucolytic drugs non-selectively reduce viscosity and elasticity of respiratory tract secretion by reducing polymer network that is responsible for the gel-like structure of mucus or sputum. Classic mucolytic disrupts mucin polymer by breaking disulfide bond connecting mucin monomer covalently into a long and rigid oligomer or by dispersing tangled mucin through breaking the bond of hydrogen ions or van der Waals.\(^6\)

The only mucolytic approved in the United States and Canada is dornase alfa. This drug is given through inhalation with a dose of 2.5 mg/day. A study showed that dornase alfa reduced viscosity and adhesion of respiratory tract secretions and long-term use could increase pulmonary function, reduced damage to lung function, and reduced the need for hospitalization and antibiotic therapy.\(^6\)

### Antibiotic

Antibiotic is only effective to cough caused by a bacterial infection, marked by purulent sputum (e.g. in suppurative bronchitis, bronchiectasis, exacerbated COPD, purulent rhinitis, and sinusitis). It is not indicated for acute bronchitis.\(^4,6\)

### 2. Non-Pharmacology

Respiratory tract cleansing may be disrupted in patients with cough mechanism abnormality (e.g. muscle weakness), mucus rheological changes (e.g. cystic fibrosis), and mucociliary clearance changes (e.g. bronchiectasis). Various efforts in increasing respiratory clearance are performed to increase pulmonary mechanism and gas exchange and to prevent atelectasis and infection, albeit lacking evidence on benefits.\(^6,7\) Cough and huffing are forced expiration maneuvers and examples of ways to cleanse respiratory tract secretions.\(^18\)

Cough physiotherapy is a technique to:

1. Increase effectiveness of cough with effective cough technique,
2. Suppress productive cough involuntarily,
3. Instruct patients to increase the use of physiotherapy tools such as acapella.\(^7\)

Several other interventions such as huffing can also be performed with the help of health workers (directed maneuver), though other interventions can be performed without help.\(^18\) Huffing is an expiration technique through the mouth with the opened esophagus, unlike cough. It helps cleanse phlegm from the respiratory tract for relief. Huffing is conducted by rapidly squeezing air in the lungs and let it out through the open mouth and esophagus like when trying to blow glass. We use the abdominal muscles to help ejecting air out without force to avoid wheezing and shortness of breath. Huffing is always followed by breathing control.\(^18,19\)

There are two huffing techniques available to help eliminate phlegm from the lungs:

1. **Small-long huff or medium-volume huff**
   This technique helps excrete phlegm from the lower chest. Take a short to moderate breath, then let the air out rapidly until the lungs feel empty.\(^18,19\)
2. Big-short huff or high-volume huff
   This technique helps excrete phlegm from the upper chest. Huff when the phlegm is near the exit. Take a deep breath and exhale quickly. This will help cleanse phlegm without coughing.\textsuperscript{18,19} Perform huffing only 1-2 times because repeated huffing can cause shortness of breath. Listen to any crackles when huffing, which indicates that cough is needed to cleanse secretion. Avoid excessive coughing because it reduces huffing effectiveness and is exhausting. Repeat the cycle for 10-15 minutes until the chest feels relieved.\textsuperscript{19}

**SUMMARY**

Cough is the most effective defense mechanism to eliminate foreign materials, including various pathogens from the respiratory tract. Cough is needed to cleanse the respiratory tract from mucus and secretions (around 20-30 ml per day). The amount of respiratory secretions depends on the number of daily exposures to irritants. A persistent cough is dangerous due to its effect on breathing, social activity, and sleeping, reducing the quality of life and cause embarrassment while socializing. It can also cause syncpe, urine incontinence, muscle pain, insomnia, and fatigue.

A cough begins with a series of breathing maneuvers which triggers sudden expulsion of air. Its mechanism is divided into three phases, i.e. inspiration, compression, and expiration phase. Cough occurs as a response to a reflex arc complex stimulation started by an irritation to the cough receptors in the trachea, carina, large respiratory tract branch, small respiratory tract, and the pharynx. These receptors can be mechanical or chemical. Cough can be caused by disruption from the pulmonary or extrapulmonary.

Cough is classified into acute, subacute, and chronic according to the duration. Acute cough occurs for a maximum of 3 weeks; subacute cough occurs within 3-8 weeks, while chronic cough occurs for more than 8 weeks. The management of cough refers to the classification and underlying cause of cough. If the cause is difficult to identify, symptomatic therapy including the administration of cough-suppressing medicines is beneficial to improve quality of life.

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