

Review

Mechanisms of fever in humans

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Accepted 22 April, 2013

This review examines the mechanisms of fever in humans. Persistent fever that cannot be explained after repeated routine clinical inquiries is called fever of unknown origin. Fever may be provoked by many stimuli. Most often, they are protozoans, bacteria and their endotoxins, viruses, yeasts, spirochets, immune reactions, several hormones, medications, and synthetic polynucleotides. These substances are commonly called exogenic pyrogens. Cells stimulated by exogenic pyrogens centrally affect the thermosensitive neurons in the preoptic area of the hypothalamus, increase the production of heat and decrease in heat loss. The body temperature increases until it reaches the set point. This information is transferred by temperature of blood that flows around the hypothalamus. The decrease of temperature is controlled by activation of mechanisms regulating increased outcome of heat to the surrounding area. Increased outcome continues in favourable case until the new equilibrium is achieved. The most important endogenous pyrogens are IL-1, IL-6 and cachectin also called tumour necrosis factor- (TNF-1). These are glycoproteins that also have other important effects. They are produced especially by monocytes and macrophages but also by endothelial cells and astrocytes. The interferons also display pyrogenic activity. Pyrogens, PGE2 release and hypothalamus play major roles in the pathophysiology of fever mechanisms.

Key words: Mechanisms. fever. humans.

INTRODUCTION

Fever also known as pyrexia (Axelrod and Diringler, 2008) is a common medical sign characterized by an elevation of temperature above the normal range of 36.5 -37.5°C (98- 100° F) due to an increase in the body temperature regulatory set point (Karakitsos and Karabinis, 2008). This increase in set point triggers increased muscle tone and shivering.

Fever is a natural reaction during a number of illnesses. In several cases, absence of the natural reaction is a more alarming sign than the presence of fever itself. Fever is usually accompanied by different general symptoms, such as sweating, chills, sensation of cold and other subjective sensations. Missing of these symptoms during high temperature may be a sign of a serious illness.

Causes of fever include infections caused by parasites, viruses, bacteria, rickettsia, Chlamydia, immune reactions (including the defects in collagen, immunological abnormalities and acquired immunodeficiency. Other

causes of fever are destruction of tissues, such as trauma, local necrosis (infarction), and inflammatory reaction in tissues and vessels (flebitis, arthritis), pulmonary infarction, and rhabdomyolysis.

Specific inflammations (sarcoidosis, granulomatous hepatitis), inflammation of intestine and intraabdominal inflammatory processes with the participation of lymphoendothelial system and hemopoetic system, solid tumours(Grawitz tumour of the kidney, carcinoma of the pancreas, pulmonary and skeletal tumours, hepatoma) can also cause fever.

Fever is present in complications of solid tumour, usually in metastases that are associated with necrosis of the tumour, obstruction of ducts, or with infection. Acute metabolic failures such as arthritis urica, porphyria, addison's crisis, thyreotoxic crisis, and feochromocytoma, administration of some drugs, dehydration and administration of salts (that is why fever occurs with diarrhea), administration of foreign proteins (e.g.

globulinum antitetanicum- antitoxic fraction of horse serum) may be the reason of fever's origin
<http://nic.sav.sk/logos/books/scientific/node47.html>.
<http://nic.sav.sk/logos/books/scientific/node48.html>.

.A typical malaria fever attack starts with a cold stage (rigor) which the patient shivers and feels cold, even though his or her temperature is rising. A hot stage follows in which the temperature rises to its maximum, headache is severe and there are back and joint pains, vomiting and diarrhea. A later stage is when the patient perspires, the temperature falls, headache and other pains are relieved, and the patient is exhausted. A major characteristic feature of malaria is fever caused by the release of toxins when erythrocytic schizonts mature which stimulate the secretion of cytokines into the cells.

The early stages of the fever is irregular and continuous. As the cycles synchronize, fever begins to recur at regular intervals especially in quartan malaria by *Plasmodium falciparum* and *Plasmodium ovale* malaria every 48 hours (<http://nic.sav.sk/logos/books/scientific/node49.html>).

Enteric fever (typhoid and paratyphoid) with bacteraemia caused by *Salmonella typhi* (most serious form) and *Salmonella paratyphi* ABC has symptoms of persistent high fever and high incidence in *Schistomiasis* endemic areas. An immune complex disorder of the kidneys can occur in those with urinary *Schistomiasis* (nephrottyphoid), characterized by fever, oedema, marked albuminuria and haematuria (<http://nic.sav.sk/logos/books/scientific/node45.html>).

The mechanisms of the different kinds of fever situations like remittent fever, quartan fever, intermittent fever, febrile (neutropenic) fever, quotidian fever, tertian fever, hyperpyrexia, continuous fever, and febricular (low-grade fever) are covered by this review which will help in the understanding and treatment of the disease.

BODY HEAT PRODUCTION

Heat is lost from the body in several ways. The biggest loss is by conduction. It depends on the gradient between the body temperature and the temperature of the surrounding environment.

The second way is by radiation. The third way is by evaporation. It is used especially during increased production of heat. Distribution of heat is done by blood circulation. Heat goes from each cell to the surrounding liquid and afterwards to the circulated blood. Modulating factor of heat loss is the amount of blood that circulates through the body surface.

The big flow through the subcutaneous area and the skin secures the incoming heat that may be given to the environment through the body surface.

Sweating helps in delivering the heat. Sweat glands are controlled by cholinergic impulses through the sympathetic fibers. During intensive sweating, up to one

liter of sweat may be formed. When the humidity of the environment is higher, a loss of heat by sweating is easier. When it is necessary to accumulate the heat in the body, adrenergic stimuli causes reduction of the blood flow through the skin. The skin becomes an isolator decreasing the heat loss to minimum control.

Control mechanisms regulate the production of heat and its loss. Production and handover (loss) of heat are controlled from the center in the hypothalamus. The hypothalamus works on the principle of negative feedback control and includes receptors registering central temperature, effector mechanisms composed of vasomotors, metabolic effectors, and control of sweat glands and also structures recording whether the actual temperature is not too high or too low.

Increased central temperature activates mechanisms enabling the heat loss. Low central temperature activates mechanisms enabling the accumulation of heat. These mechanisms work as a thermostat (<http://www.gpnotebook.co.uk/>). There are two key physiological mechanisms for increasing heat loss from the body of man. They are sweating and vasodilation. Generally, both act in tandem to lower core temperature under the integration of the hypothalamus. However, there may be situations when either mechanism is inefficient or disordered e.g. high external humidity or anticholinergic drugs for sweating, and the use of alpha-adrenoceptor blocking drugs for vasodilatation.

Decreased heat production is a theoretical means of decreasing temperature. In practice, the metabolic rate is unchanged, the only contribution to decreasing temperature is an inhibition of shivering and non-shivering thermogenesis.

This is not as important as sweating and vasodilatation (<http://www.gpnotebook.co.uk/>). The main task of heat production has thermogenesis caused by the effect of thyroid hormones. Hormones of thyroid gland stimulate the cytoplasmic membranes. Increased production of heat is achieved by increasing the metabolic processes in which energy is release in the form of heat.

The Basal Metabolic rate (BMR) is defined as the heat production of a human being in a thermoneutral environment (33°C or 91°F) and at rest mentally and physically more than 12 hours after the last meal. The standard BMR for a 70kg man is approximately 1.2 W/kg, but it can be altered by changes in active body mass, diet, and endocrine levels. It is probably not affected by living in hot climates. The range of endogenous heat production, M, dependent on the work being performed, age, sex, size, physical fitness, and level of activity, is about 40 to 800 W/m² (or 1-21 W/kg for a standard man

. If deep body temperature is altered, either by heat storage from being in a warm environment, or by febrile disease (having a fever), then M changes as well. In cold environments , for example, shivering induced by the body can increase heat production up to four or five times

the normal resting level. Further increase can be induced by exercise (<http://www.deas.harvard.edu>).

BODY TEMPERATURE

If the body temperature is above 37.2°C and is associated with sweating, hyperventilation and vasodilation in the skin, we speak of fever. At the beginning, gradual increase in body temperature is observed together with muscle shivering, vasoconstriction in the skin, and piloerection. This situation is called chills. Increased body temperature is achieved by lowered loss of heat.

Vasoconstriction in the skin and subcutaneous tissue is the cause of pale colour and dryness. The affected person has a feeling of coldness. At the same time, the production of heat in the body increases. The muscle tonus increases, the spasms occur. Spasms may occur only in children. When the vasodilation starts in the skin, the feeling of warmth and sweating occurs. As a person's temperature increases, there is, in general, a feeling of cold despite an increasing body temperature. Once the new temperature is reached, there is a feeling of warmth. Temperature sensation rests with receptors in the three key sites which includes peripheral thermoreceptors present in the skin as free nerve endings of A and C type fibres, central thermoreceptors which are two types of receptors found in the preoptic area of the anterior hypothalamus. One group responds to relative warmth, the other to relative cold. Other sites are the spinal cord, abdominal viscera and great veins (<http://www.gpnotebook.co.uk/>).

A fever can be caused by many different conditions ranging from benign to potentially serious. There are arguments for and against the usefulness of fever, and the issue is controversial. With the exception of very high temperatures, treatment to reduce fever is often not necessary; however, antipyretic medications can be effective at lowering the temperature, which may improve the affected person's comfort.

Fever differs from uncontrolled hyperthermia (Axelrod and Diringer, 2008) in that hyperthermia is an increase in body temperature over the body's thermoregulatory set-point, due to excessive heat production and /or insufficient thermoregulation.

Low body temperature and hypothyroidism is more common than is typically diagnosed. It is possible to have some laboratory values be returned in the normal range when we have low thyroid symptoms. Oral temperatures during the day of less than 98.0 °F (36.7°C) are very suspicious. Wilson's syndrome is a state of chronic low body temperature. It may be genetic, or triggered by stress or inactivity, as well as diet, selenium or zinc deficiency, heavy metals or starvation. It appears to be part of the body's method of conserving fuel.

Wilson's syndrome occurs when someone drops into

this conservation mode and is not able to later recover back to the normal productive mode of functioning. An interesting side note is that Dr. Fahrenheit considered normal body temperature to be 100 °F. Some say that the present average temperature is 98.2 °F and may be lower than it was 150 years ago.

HYPOTHALAMUS

Homeostasis is the ability or tendency of an organism or cell to maintain internal equilibrium by adjusting its physiological processes. Our normal body temperature, for example, is around 98.6 °F. If we start to get cold, we shiver. Shivering is a physiological process designed to keep our body temperature from dropping below 98.6 °F. Also, we may put a coat on. This will also help to keep our body temperature from dropping, but it is not a physiological process. Our body has many physiological processes designed to maintain many equilibriums.

Homeostasis is the tendency for individuals to maintain their internal environment (e.g. body temperature) fairly constant. One of the most obvious examples of homeostasis is body temperature which in humans is normally very close to 98.6 °F or 37°C (<http://www.psypress.co.uk>).

In humans, temperature homeostasis is controlled by the thermoregulatory center in the hypothalamus. The hypothalamus is a group of neurons, at the base of the brain, and forms the primary link between the nervous system and the endocrine system. Among the homeostatic processes controlled by the hypothalamus are: thirst, hunger, daily (circadian) rhythms, body temperature and blood pressure (<http://www.newton.dep.anl.gov>). The hypothalamus receives inputs from two sets of thermoreceptors: receptors in the hypothalamus itself which monitor the temperature of the blood as it passes through the brain (the core temperature), and receptors in the skin that monitor the external temperature. Both pieces of information are needed so that the body can make appropriate adjustments.

The thermoregulatory center sends impulses to several different effectors to adjust body temperature¹². Heat is sensed by the skin and the hypothalamus, as both contain thermoreceptors. External environment temperature is sensed by the skin, and the internal environment temperature is sensed by the hypothalamus. When it is cold outside, messages are sent from the thermoreceptors in the skin or from deep thermal receptors or via the blood to the cerebrum and the hypothalamus. The cerebrum makes the person aware of being cold, and can cause behavioural changes which are voluntary, for example, to put on a sweater. When the message has reached the hypothalamus, a series of reactions follow.

TRH (thyroid releasing hormone) is released by the

hypothalamus, its target organ being the anterior lobe of the pituitary gland. It releases TSH (thyroid stimulating hormone) into the blood stream. The target organ of TSH is the thyroid gland. Upon receiving TSH, the thyroid then produces thyroxin. Thyroxin increases cellular metabolism to make heat.

Other things that happens includes vasoconstriction (blood diverted from skin to keep heat), reduced sweating, skin hairs raised (erectile pilli muscle contracted), shivering and increased metabolic rate. When it is too warm, messages are sent in the same way to the hypothalamus. This causes increased sweating to release heat via water, vasodilation (blood diverted to skin to lose heat), skin hairs lowered and reduced metabolic rate (<http://www.revision-notes.co.uk/revision/858.html>).

The brain ultimately orchestrates heat effector mechanisms via the autonomic nervous system. This will increase heat production by increased muscle tone, shivering, and hormones like epinephrine, and also prevention of heat loss, such as vasoconstriction .In infants, the autonomic nervous system may also activate the adipose tissue to produce heat (non-exercise-associated thermogenesis, also known as non-shivering thermogenesis). Increased heat production rate and vasoconstriction contribute to increased blood pressure in fever (<http://www.revision-notes.co.uk/revision/858.html>).

PYROGENS

Substances that cause fever are known as “pyrogens”. There are two types of pyrogens; exogenous and endogenous pyrogens. Those that originate outside the body, such as bacteria toxins, are called “exogenous pyrogens. Pyrogens formed by the body’s own cells in response to an outside stimulus (such as bacteria toxins) are called endogenous pyrogens.

A pyrogen is a substance that induces fever. These can be either internal (endogenous) or external (exogenous) to the body. The bacterial substance lipopolysaccharide (LPS), present in the cell wall of some bacteria, is an example of an exogenous pyrogen.

Pyrogenicity can vary: In extreme examples, some bacterial pyrogens known as superantigens can cause rapid and dangerous fevers. Depyrogenation may be achieved through filtration, distillation, chromatography, or inactivation.

In essence, all endogenous pyrogens are cytokines, molecules that are part of the innate immune system. They are produced by phagocytic cells and cause the increase in thermoregulatory set-point in the hypothalamus. Major endogenous pyrogens are interleukin 1 (alpha and beta) (Walter, 2003) interleukin 6 (IL-6) and tumor necrosis factor –alpha. Minor endogenous pyrogens include interleukin-8, tumour necrosis factor-alpha, tumour necrosis factor-beta, macrophage

inflammatory protein-alpha and macrophage inflammatory protein –beta as well as interferon-alpha, interferon-beta and interferon- gamma (Walter, 2003).

These cytokine factors are released into general circulation, where they migrate to the circumventricular organs of the brain due to easier absorption caused by the blood-brain barrier’s reduced filtration action there. The cytokine factors then bind with endothelial receptors on vessel walls, or interact with local microglial cells.

When these cytokine factors bind, the arachidonic acid pathway is then activated. One model for the mechanism of fever caused by exogenous pyrogens includes LPS, which is a cell wall component of gram-negative bacteria. An immunological protein called lipopolysaccharide-binding protein (LBP) binds to LPS. The LBP-LPS complex then binds to the CD14 receptor of a nearby microphage.

This binding results in the synthesis and release of various endogenous cytokine factors, such as interleukin 1(IL-1), interleukin 6 (IL-6), and the tumour necrosis factor-alpha. In other words, exogenous factors cause release of endogenous factors, which in turn, activate the arachidonic acid pathway.

Researchers have discovered that there are several “endogenous pyrogens”. These are made up of small groups of amino acids, the building block of proteins. These natural pyrogens have other functions in addition to inducing fever; they have been named “cytokines”. When cytokines are injected into humans, fever and chills develop within an hour. Interferon, tumour necrosis factor, and various interleukins are the major fever producing cytokines. The production of fever is a very complex process; somehow, these cytokines cause the thermoregulatory center in the hypothalamus to reset the normal temperature level. The body’s initial response is to narrow and prevent heat loss from the skin and elsewhere. This alone will raise the temperature by two to three degrees. Certain behavioural activities also occur, such as adding more clothes, seeking a warmer environment, etc. If the hypothalamus requires more heat, then shivering occurs (<http://www.healthatoz.com>).

RELEASE OF PGE2

prostaglandin E2 (PGE2) release comes from the arachidonic acid pathway. This pathway (as it relates to fever), is mediated by the enzymes phospholipase A2 (PLA2), cyclooxygenase-2 (COX-2), and prostaglandin E2 synthase. These enzymes ultimately mediate the synthesis and release of PGE2. PGE2 is the ultimate mediator of the febrile response. The set-point temperature of the body will remain elevated until PGE2 is no longer present. PGE2 acts on neurons in the preoptic area (POA) through the prostaglandin E receptor 3 (EP3). EP3- expressing neurons in the POA innervate the dorsimedial hypothalamus (DMH), the rostral raphe

pallidus nucleus in the medulla oblongata (rRPa), and the paraventricular nucleus (PVN) of the hypothalamus.

Fever signals sent to the DMH and RPa lead to stimulation of the sympathetic output system, which evokes non-shivering thermogenesis to produce body heat and skin vasoconstriction to decrease heat loss from the body surface. It is presumed that the innervation from the POA to the PVN mediates the neuroendocrine effects of fever through the pathway involving pituitary gland and various endocrine organs.

Temperature is ultimately regulated in the hypothalamus. A trigger of the fever, called a pyrogen, causes a release of prostaglandin E2 (PGE2). PGE2 then in turn acts on the hypothalamus, which generates a systemic response back to the rest of the body, causing heat-creating effects to match a new temperature level. In many respects, again, the hypothalamus works like a thermostat¹⁶. When the set-point is raised, the body increases the temperature through both active generation of heat and retaining heat. Vasoconstriction both reduces heat loss through the skin and causes the person to feel cold. If these measures are insufficient to make the blood temperature in the brain match the new setting in the hypothalamus, then shivering begins in order to use muscle movements to produce more heat. When the fever stops, and the hypothalamic setting is set lower; the reverse of these processes (vasodilation, end of shivering and nonshivering heat production) and sweating are used to cool the body to the new, lower setting. This contrasts with hyperthermia, in which the normal setting remains, and the body overheats through undesirable retention of excess heat or over-production of heat (Fauci, 2008).

Hyperthermia is usually the result of an excessively hot environment (heat stroke) or an adverse reaction to drugs. Fever can be differentiated from hyperthermia by the circumstances surrounding it and its response to anti-pyretic medications.

CONCLUSION

Pyrexia is from the Greek *pyr* meaning *fire*. Febrile is from the Latin word *febris*, meaning *fever*, and archaically known as *ague*. Fever phobia is the name given by medical experts to parents' misconceptions about fever in their children. Among them, many parents incorrectly believe that fever is a disease rather than a medical sign, that even low fevers are harmful, and that any temperature even briefly or slightly above the oversimplified "normal" number marked on a thermometer is a clinically significant fever¹⁷. They are also afraid of harmless side effects like febrile seizures and dramatically overestimate the likelihood of permanent damage from typical fevers (Crocetti et al., 2001). The underlying problem, according to professor of pediatrics Barton D. Schmitt, is "as parents, we tend to suspect that our children's brains may melt" (Klass, 2011). As a result

of these misconceptions, parents are anxious, give the child fever-reducing medicine when the temperature is technically normal or when slightly elevated, and interfere with the child's sleep to give the child more medicine (Crocetti et al., 2001).

Fever is a common symptom of many medical conditions like infectious diseases, e.g., influenza, HIV, malaria, infectious mononucleosis, or gastroenteritis, various skin inflammations, e.g. boils, or abscess, immunological diseases, e.g. , lupus erythematosus, sarcoidosis, inflammatory bowel diseases, Kawasaki disease, Tissue destruction, which can occur in hemolysis, surgery, infarction, crush syndrome, rhabdomyolysis, cerebral hemorrhage, etc., reaction to incompatible blood products, cancers, most commonly , kidney cancer and leukemia and lymphomas, metabolic disorders, e.g. gout or porphyria and Thrombo-embolic processes, e.g. , pulmonary embolism or deep venous thrombosis. Persistent fever that cannot be explained after repeated routine clinical inquiries is called fever of unknown origin.

A wide range for normal temperatures has been found¹⁹. Fever is generally agreed to be present if the elevated temperature is caused by a raised set-point and temperature in the anus (rectum/rectal) is at or over 37.5 - 38.3 °C (99.5 – 100. 9 °F) (Axelrod and Diringner, 2008; Laupland, 2009)^{1,19}, temperature in the mouth (oral) is at or over 37.7 °C (99.9 °F) (Barone, 2009), and temperature under the arm (axillary) or in the ear (otic) is at or over 37.2 °C (99.0 °F).

In healthy adult men and women, the range of normal, healthy temperatures for oral temperature is 33.2 – 38.2 °C (91.8- 100.8 °F), for rectal it is 34.4 – 37.8 °C (93.9- 100 °F) for tympanic membrane (the ear drum) it is 35.4- 37.8 °C (95.7- 100 °F) and for axillary (the armpit) it is 35.5 – 37.0 °C (95.9- 98.6 °F) (Sund- Levander et al., 2002).

Normal body temperatures vary depending on many factors, including age, sex, time of day, ambient temperature, activity level, and more. A raised temperature is not always a fever. For example, the temperature of a healthy person rises when he or she exercises', but this is not considered a fever, as the set-point is normal.

On the other hand, a "normal" temperature may be a fever, if it is usually high for that person. For example, medically frail elderly people have a decreased ability to generate body heat, so a "normal" temperature of 37.3 °C (99.1 °F) may represent a clinically significant fever.

The pattern of temperature changes may occasionally hint at the diagnosis. In continuous fever, temperature remains above normal throughout the day and does not fluctuate more than 1°C in 24 hours, e.g. lobar pneumonia, typhoid, urinary tract infection, brucellosis, or typhus. Typhoid fever may show a specific fever pattern (*Wunderlich curve* of typhoid fever), with a slow stepwise increase and a high plateau and drops due to fever –

reducing drugs are excluded. In intermittent fever, the temperature elevation is present only for a certain period, later cycling back to normal, e.g. malaria, kala-azar, pyaemia, or septicemia.

Other types are (Muhammad and Shabbir, 2009) Quotidian fever, with a periodicity of 24 hours, typical of malaria, tertian fever (48 hour periodicity), typical of malaria, quartan fever (72 hour periodicity), typical of *Plasmodium malariae*, fever that continues to abrupt onset and remission, undulant fever, relapsing fever: temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, e.g. infective endocarditis. Pel- Ebstein fever is a specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on. However, there is some debate as to whether this pattern truly exists (Hilson, 1995). A neutropenic fever, also called febrile neutropenia, is a fever that function in the absence of normal immune system because of the lack of infection- fighting neutrophils, a bacterial infection can spread rapidly; this fever is therefore usually considered to require urgent medical attention. This kind of fever is more commonly seen in people receiving immune-suppressing chemotherapy than in apparently healthy people. *Febricula* is an old term for low-grade fever, especially if the cause is unknown, no other symptoms are present, and the patient recovers fully in less than a week (Rolla, 1906).

Hyperpyrexia is a fever with an extreme elevation of body temperature greater than or equal to 41.2 °C (106.7 °F) (Loscalzo et al., 2008). Such a high temperature is considered a medical emergency as it may indicate a serious underlying condition or lead to significant side effects²⁶. The most common cause is an intracranial hemorrhage (Loscalzo et al., 2008). Other possible causes include sepsis, Kawasaki syndrome (Marx, 2006), neuroleptic malignant syndrome, drug effects, serotonin syndrome, and thyroid storm (McGugan, 2001) Infections are the most common cause of fevers, however as the temperature rises, other causes become more common (McGugan, 2001) . Infections commonly associated with hyperpyrexia include roseola, rubeola and enteroviral infections (Marx, 2006).

Immediate aggressive cooling to less than 38.9 °C (102.0 °F) has been found to improve survival (McGugan, 2001). Hyperpyrexia differs from hyperthermia in that in hyperpyrexia the body's temperature regulation mechanism sets the body temperature above the normal temperature, then generates heat to achieve this temperature, while in hyperthermia the body temperature rises above its set point (Loscalzo et al., 2008) Hyperthermia is an example of a high temperature that is not fever. It occurs from a number of causes including heatstroke, neuroleptic malignant syndrome, malignant hyperthermia, stimulants such as amphetamines and cocaine, idiosyncratic drug reactions and serotonin syndrome.

A fever is usually accompanied by sickness behaviour, which consists of lethargy, depression, anorexia, sleepiness, hyperalgesia, and the inability to concentrate (Hart, 1988; Johnson, 2002; Kelly et al., 2003).

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