Journal of Infection and Public Health (2011) 4, 108—124

http://www.elsevier.com/locate/jiph

REVIEW

# Fever, fever patterns and diseases called 'fever' — A review

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Received 19 February 2011; received in revised form 21 April 2011; accepted 8 May 2011

**KEYWORDS**
Fever;
Body temperature;
Pyrogens;
Pathogenesis;
Fever patterns;
Disease

**Summary** Fever is a prominent feature of disease since antiquity. The febrile response is orchestrated by the central nervous system through endocrine, neurological, immunological and behavioural mechanisms. Other than a regulated rise in body temperature, fever is often accompanied by various sickness behaviours, changes in metabolic and physiological characteristics of body systems and alterations in immune responses. Fever and the febrile response, therefore, remain significant contributors to the pathogenesis, clinical presentation and outcome of many illnesses and diseases.

This review highlights the pathophysiology of the febrile response and describes the fever types and patterns, including their clinical significance. The various medical illnesses called ''fever'' are also listed and the origins of their appellations discussed.



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doi:10.1016/j.jiph.2011.05.002

## Introduction

Fever is one of the oldest clinical indicators of disease in the mammalian host as well as one of the most common reasons for medical consultations worldwide [1,2]. Fever often occurs in response to infection, inflammation and trauma. However, this view of fever is merely an oversimplification as a growing body of evidence now suggests that fever represents a complex adaptive response of the host to various immune challenges whether infectious or non-infectious. Although elevated body temperature is an indispensable component of the febrile response, it is not synonymous with fever. It is generally agreed that fever is a regulated rise in body temperature above normal daily fluctuations occurring in conjunction with an elevated thermoregulatory set point [1—5]. To highlight the adaptive nature of the febrile response, the International Union of Physiological Sciences Commission for Thermal Physiology in 2001 defined fever as a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (micro-organisms) or inanimate matter recognised as pathogenic or alien by the host [6].

The complexity of the febrile response may be attributable to its multi-systemic effects orchestrated by endocrine, neurological, immunological and behavioural mechanisms. Apart from a regulated rise in body temperature, fever is also accompanied by various sickness behaviours, changes in metabolic and physiological characteristics of body systems and alterations in immune responses [2,3]. The febrile response, therefore, remains a significant contributor to the pathogenesis, clinical presentation and outcome of many illnesses and diseases. Consequently, understanding fever and febrile response is vital in the diagnosis, treatment and follow-up of various ailments and diseases.

This review gives an overview of the pathophysiology of the febrile response and describes the fever types and patterns, including their clinical significance. The various medical illnesses called ''fever'' are also listed and the origins of their appellations discussed.

## Thermoregulation

In healthy individuals, body temperature varies in relation to several environmental and biological factors such as time of day, site of temperature measurements, level of physical activity, age, sex and race, among others [2,7]. In spite of this variability, body temperature is tightly regulated within a fairly constant range-a thermal set point (recently renamed thermal balance point [8]) through the process of thermoregulation.

The old view that temperature regulation functions as a unified control system with a single thermoregulatory centre has been rejected. Based on recent evidence, core temperature is regulated by various relatively independent thermoeffector loops, each having its own afferent and efferent branches [7—9]. Hence, the regulation of body temperature is dependent on a thermoregulatory circuitry. However, the preoptic region of the anterior hypothalamus is still considered the major thermoregulatory centre in the CNS where peripheral and centrally generated temperature signals are received and integrated [7—9].

The preoptic region consists of heat sensitive neurons, namely warm and cold sensitive neurons, which are activated or inhibited in response to temperature changes. In cold environments, decrease firing of warm sensitive neurons and increase firing of cold sensitive neurons leads to activation of heat gain mechanisms and prevention of heat loss (i.e. by skin vasoconstriction, piloerection, decrease sweating, increased muscle contraction, non-shivering thermogenesis, and

seeking warm clothing or environments). In hot environments, increase firing of warm sensitive neurons and decrease firing of cold sensitive neurons leads to activation of heat loss mechanisms and inhibition of heat gain mechanisms (i.e. by sweating, removal of clothing or seeking cold environments). Ultimately, body temperature is kept within a normal regulated limit by a delicate balance between heat loss and heat gain.

## Defining normal and febrile body temperatures

Due to wide variability of body temperature in relation to several factors, defining febrile body temperatures remain a subject of controversy with varied definitions by different authors. However, most authors [2—4] are in agreement with a study in which modern calibrated thermometers were used to measure 700 baseline-oral temperatures of 148 middle aged healthy adults of different races [10]. In this study, the mean oral temperature was $36.8 \pm 0.4\,^{\circ}C$ (98.2 °F) and body temperature exhibited a circadian rhythm with 99th percentile of the population having maximum morning (at 6.00 am) of 37.2 °C and maximum afternoon (at 4.00 pm) temperature of 37.7 °C. Thus, on the basis of this study data, fever in healthy middle aged adults may be defined as early morning oral temperature of >37.2 °C (>99 °F) or a temperature of >37.7 °C (>100 °F) at anytime during the day.

Based on guidelines for management of febrile illnesses provided by authorities such as World Health Organization (WHO) [11,12] and the Society of Critical Care Medicine and the Infectious Disease Society of America (IDSA) [13], among others [14,15], equivalent rectal temperature of ≥38 °C (100.4 °F) or axillary temperatures of ≥ 37.5 °C (99.5 °F) are indicative of fever in both adults and children. However, as compared to older children and adults, infants and young children experience higher and more prolonged fevers, more rapid temperature increases, and greater temperature fluctuations [15]. In the geriatric group (>65 years), who are likely to have lower body temperatures, IDSA defines fever as single oral temperature >100 °F (>37.8 °C); or (2) repeated oral temperatures >99 °F (>37.2 °C) or rectal temperatures >99.5 °F (>37.5 °C); or (3) an increase in temperature of >2 °F (>1.1 °C) over the baseline temperature [16].

Of the three major sites (i.e. rectal, oral and axillary) used for temperature assessment, rectal temperatures more closely estimate core temperatures than oral temperatures or axillary temperatures [2,8]. Although, axillary temperatures are convenient to undertake, they are the least accurate method of temperature measurement, especially in adults. Axillary thermometers take longer time to reach equilibrium and they are altered by various factors such as by ambient temperature, sweat, humidity and the density of hair in the axilla [2,8].

## Pathophysiology of the febrile response

The development of the febrile response is akin to the normal thermoregulatory processes that follow exposure to cold temperatures. However, in fever the thermal balance point is reset to a higher level such that normal peripheral and central body temperatures are now sensed as cold temperature signals by the thermoregulatory circuitry [2—5]. Consequently, fever is different from heat stroke and hyperthermia where body temperature is elevated without a corresponding elevation of the thermal balance point.

Like thermoregulation, evolving evidence suggest that the generation of fever follows multiple independent afferent and efferent mechanisms depending on the site, nature and severity of inflammation. The various biological molecules involved in the generation of the febrile response and the pathways implicated in these responses are discussed in the following section.

## Fever: the role of pyrogens and cryogens

The initiation, manifestations and regulation of the febrile response are dependent on the pyrogenic and anti-pyretic properties of various exogenous and endogenous substances [2,17,18]. While pyrogens directly or indirectly lead to fever, cryogens prevent excessive temperature elevation. It is the balance in the interactions between pyrogens and cyrogens that determine the height and duration of the febrile response to any immune challenge.

### Pryogens

Pyrogens are classified into exogenous (produced outside the host) and endogenous (produced within the host) pyrogens based on their site of production. Exogenous pyrogens are, essentially, part or whole micro-organisms or products of micro-organisms such as toxins. The gram negative cell wall component —lipopolysaccharide (LPS), remains the most widely studied exogenous pyrogen and most of the current data of the febrile response are based on studies using LPS as the pyrogenic

agent. Other clinical significant endogenous pyrogens include muramyl dipeptidase — a constituent of cell walled micro-organisms, and enterotoxins of *Staphylococcus aureus* and group A and B *Streptococcus* collectively named superantigens [2,4].

Endogenous pyrogens are mainly pyrogenic cytokines including interleukins (IL) 6, IL-1, interferon gamma (INF-$\gamma$) and ciliary neurotropic factor (CNTF) and tumour necrosis factor (TNF $\alpha$), among others [2,4]. However, TNF $\alpha$ has both pyrogenic and antipyretic actions depending on experimental conditions [17]. Endogenous pyrogens are produced by immune cells such as neutrophils, macrophages and lymphocytes as well as by endothelial cells, astrocytes and glial cells in response to exposure to exogenous pyrogens. Certain endogenous substances such as antigen-antibody complexes, inflammatory bile acids, complements and various lymphocyte derived molecules may however serve as pyrogens without induction by exogenous pyrogens [2].

### Cryogens

Cyrogens include anti-inflammatory cytokines (e.g. IL-10), hormones (e.g. $\alpha$-melanocyte stimulating hormone, corticotrophin and corticotrophin releasing hormone) and many other neuroendocrine products (e.g. neuropeptide Y, bombesin, and thyroliberin), cytochrome P-450 (P-450), among others [2,17,18]. They exert their anti-pyretic effects by inhibiting synthesis of pyrogenic cytokines (e.g. glucocorticoids), cytokine receptors blockade (e.g. IL-1 receptor antagonist), and increasing heat loss by enhancing sensitivity of warm sensitive neurons (e.g. bombesin) [2], among other mechanisms. These endogenous antipyretic systems protect the host against the destructive consequences of unchecked fever.

## The fever pathways

Fever signals carried by exogenous and endogenous pyrogens ultimately lead to reset of the thermoregulatory circuitry via two basic pathways, namely the humoral and neural pathways (reviewed in Refs. [19—21]).

### The humoral pathway

In this pathway, fever signals are carried by components of microbial products named pathogen associated molecular patterns (PAMPS) or by pyrogenic cytokines.

Circulating PAMPS of micro-organisms, typified by gram negative LPS, are known to bind toll like receptors 4 (TLR-4) on various cells [22]. By binding to and activating TLR-4 located on the fenestrated capillaries of the circumventricular organ in the blood brain barrier, they lead to release of prostaglandin E2 (PGE2) from the arachidonic acid pathway in cytoplasmic membranes [22—24]. Prostaglandin E2 is small molecule that easily diffuses across the blood brain barrier, binds to specific PGE2 receptors (EP3 receptor) in the preoptic area and then activates thermal neurons in the anterior hypothalamus to a higher thermal balance point [2,22—24]. It is unclear whether microbial products also lead to elevation of the thermal balance point by gaining direct access to the brain through disruption of the BBS.

The febrile response is characterised by an early rapid phase and a delayed late phase. Based on studies undertaken in animal models with polyphasic LPS-induced fever, it is believed that the first phase of this febrile response is dependent on PGE2 synthesized in the liver and lungs before migration to the brain, while the latter phases are due to centrally synthesized PGE2 [25,26]. Consequently, while peripheral synthesized PGE2 may act to initiate the febrile response, centrally synthesized PGE2 may be largely involved in its maintenance.

The second humoral pathway is directed by circulating pyrogenic cytokines. They transmit fever signals to the thermoregulatory circuitry by both indirect and direct pathways. In the indirect pathway, pyrogenic cytokines act outside the brain by binding and activating cytokine receptors located on the fenestrated capillaries of the circumventricular organ leading to release of PGE2 [2,3,27]. In the direct pathway, circulating cytokines disrupt the blood brain barrier gaining direct access to cytokine receptors expressed on vascular, glial and neuronal structures of the brain [27]. Activation of these central receptors stimulates further synthesis of PGE2 or promotes de novo synthesis of more cytokines by the brain.

Although PGE2 remains fundamental in the febrile response, some cytokines and many other inflammatory mediators may activate the febrile response independent of PGE2 [19]. Direct PGE2-independent activation of the thermal neurons by cytokines may be responsible for the hyperpyrexia seen in CNS infections and haemorrhages — the latter also referred to as central fever [3]. In these conditions, the anti-pyretic properties of the CNS are disrupted, leading to unregulated rise in body temperature. Examples of inflammatory mediators, other than PGE2, that may reset the thermal balance point independent of PGE2 include, bradykinin, corticotrophin releasing hormone, nitric oxide, MIP-1, IL-6, and IL-8, preformed pyrogenic factors (PFPF), substance P and endothelin-1 [19].

**The neural pathway**

Peripheral fever signals can communicate with the CNS through peripheral nerves such as cutaneous sensory nerves and the vagus nerve. The activation of the neural pathway is believed to be another mechanism by which fever is rapidly initiated [19—21].

It has been suggested that localised formation of PGE2 at sites of inflammation contribute to fever generation by activating cold-sensitive cutaneous nerves, which, in turn, transmit fever signals to parts of the brain responsible for fever generation [28]. The transmission of fever signals via the vagus nerve follows a more complex pathway. Circulating pyrogens such as LPS activate complement and complement products in turn stimulate Kupffer cells of the liver to produce endogenous mediators including pyrogenic cytokines. These cytokines activate the hepatic branch of the vagus nerve which then transmits fever signals to the central projection of the area of the vagus nerve within the nucleus of tractus solitarius (NST). From the NST, the signal proceeds to the preoptic and hypothalamic areas via the ventral noradrenergic bundle, causing the intrapreoptic release of norepinephrine [19,21].

Norepinephrine mediates the vagal pathway by evoking distinct core temperature rises. The first is alpha (1)-adrenoceptor (AR)-mediated, rapid in onset, and PGE2-independent, while the second is alpha (2)-AR-mediated, delayed, and PGE2-dependent [19,21].

The role of vagal afferents in fever generation was based on experimental studies in rats which showed that surgical vagotomy lead to attenuation or complete abortion of febrile responses to pyrogenic signals [19,20]. However, more recent studies have challenged this view, attributing the lack of febrile response to pyrogenic signals to the side effects of vagotomy, such as malnutrition [29,30]. When such side effects of vagotomy are avoided, experimental studies in rats suggest that complete or partial vagotomy did not abort the febrile response to pyrogenic signals such as intravenous PGE2 [29].

## Symptoms of fever

The reset of the thermal balance point to a higher level by humoral and neural fever signals described above initiates a feedback loop that lead to sequence of clinical and behavioural manifestations that characterise the febrile response. To meet the new balance point, heat loss is inhibited by skin vasoconstriction (leading to chills and goose pimples), as well as by behavioural mechanisms such as assuming a fetal position to reduce body surface area or wearing thick clothing and seeking warmer environments [2,5]. Various heat gain mechanisms are then activated including increase muscle contraction (leading to rigors). When the fever signal is no longer present in the CNS, the balance point drops to normal with activation of heat loss mechanisms such as sweating. Hence, fever is often characterised by chills, rigors, rise in body temperature and subsequently sweating and fall in body temperature.

Systemic symptoms such as headache, malaise, anorexia and other sickness behaviours may also accompany fever. These symptoms are due to the systemic effects of microbial products and pyrogenic cytokines that lead to various acute phase responses mediated through the neuroendocrine system [2,5]. Fig. 1 gives a summary of the pathways leading to fever and associated acute phase responses.

## Classification, types and patterns of fever

Fevers can be arbitrary classified into acute, sub-acute and chronic fevers based on duration. Acute fevers (<7 days in duration) are characteristics of infectious diseases such as malaria and viral-related upper respiratory tract infection while sub-acute fevers (usually not more than 2 weeks in duration) may be seen in cases of typhoid fever and intra-abdominal abscess, among others [3]. Chronic or persistent fevers (>2 weeks duration) are typical of chronic bacterial infections such as tuberculosis, viral infections like HIV, cancers and connective tissue diseases [3]. However, any cause of acute fever can become persistent or chronic if untreated.

Based on the height of body temperature, fever can also be classified into low grade, moderate grade, high grade and hyperpyrexia (Table 1)[31,32]. The height of body temperature may have some diagnostic and prognostic implications. Some studies have attributed high grade fevers in infants to serious bacterial infections [33], although others have also shown that children with high fevers are at equally high risk for serious bacterial infections and for viral illness [34].

The height of fever may occasionally correlate with severity of illness, as suggested in experimental shigellosis and dengue virus infection [35,36], as well as in acute falciparum malaria where presence of hyperpyrexia denotes complicated disease with

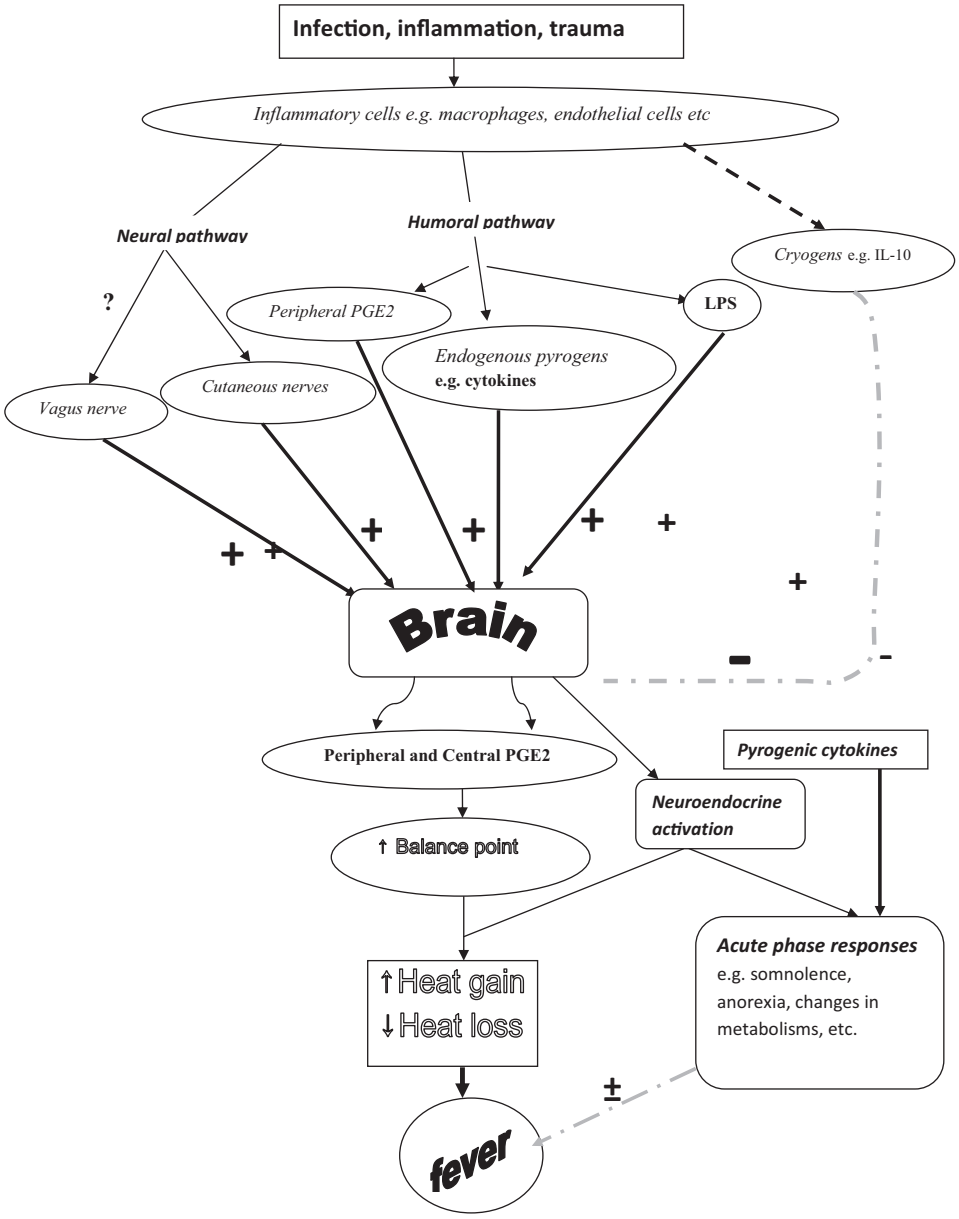


**Figure 1** Illustration of the pathways leading to fever. *Legend*: Following infection, inflammation or trauma, immune cells activate the release of pyrogenic cytokines as well as cryogens. Fever signals are transmitted via neural and humoral pathways to the brain to reset the thermal balance point. Vagal afferents may not necessarily be involved in fever generation. Cryogens prevent excessive elevation of the balance point. Heat gain mechanisms and acute phase responses are activated whereas heat loss is minimised. Ultimately, body temperature rises to new thermal balance point producing fever. *Key*: LPS-Lipopolysaccharide, ''+'' activate,''-'' inhibit, ''?'' contentious.

poor prognosis [37]. However, the overall clinical state of the patient is a more powerful predictor of serious illness than the height of the fever [15].

Three major fever types have been described including sustained/continuous fever, intermittent fever and remittent fever [31,38]. Figs 2 and 3 illustrate these major fever patterns. Continuous or sustained fever is defined as fever that does not fluctuate more than about 1 °C (1.5 °F) during 24 h, but at no time touches normal [38]. Continuous fevers are characteristics of lobar and gram-negative pneumonia, typhoid, acute bacterial meningitis, urinary tract infection, among others [31]. Fever characterised by slow stepwise temperature rise and a high plateau are classical of typhoid fever (Fig. 2) [39]. However, this fever pattern is reported in only about 12% of cases in clinical practice [39], possibly because most patients with fever self-medicate with antibiotics and anti-pyretics before consulting a health

**Table 1** Normal and febrile body temperature ranges (rectal temperatures).

| Body temperature | °C | °F |
|---|---|---|
| Normal | 37—38 | 98.6—100.4 |
| Mild/low grade fever | 38.1—39 | 100.5—102.2 |
| Moderate grade fever | 39.1—40 | 102.2—104.0 |
| High grade fever | 40.1—41.1 | 104.1—106.0 |
| Hyperpyrexia[a] | >41.1 | >106.0 |

Data from Refs. [31,32]. NB—hypothermia = rectal temperature <35 °C (<95 °F).

[a] Hyperpyrexia in severe malaria is defined as rectal temperature above 40 °C [33]. C, centigrade; F, Fahrenheit.

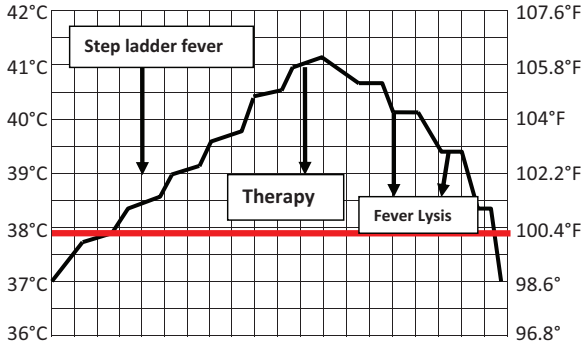


**Figure 2** Continuous step ladder pattern of fever classical of typhoid fever. *Legend*: Continuous fevers do not fluctuate more than about 1 °C (1.5 °F) during 24 h, but at no time touches normal. Following effective therapy of typhoid fever, fever defervescence occurs gradually, by lysis.

personnel. Fever associated with relative bradycardia (temperature pulse dissociation or Faget's sign) is a feature of untreated typhoid, leishmaniasis, brucellosis, Legionnaire's disease and psittacosis, Yellow Fever, among others [40].

Intermittent fever is defined as fever present only for several hours during the day [38]. This pattern of fever can be seen in malaria, pyogenic infections, tuberculosis (TB), schistosomiasis, lymphomas, leptospira, borrelia, kala-azar, or septicemia [31]. Sources of continuous, intermittent or transient bacteraemia may lead to continuous, intermittent or transient fevers respectively. In malaria, depending on the specie of parasite, fever can occur with a periodicity of 24 h (quotidian- due to plasmodium falciparum), 48 h (tertian — plasmodium ovale and vivax), or 72 h (quartan — *Plasmodium malariae*) [31]. The Pel-Epstein's fever is an intermittent low grade fever characterised by 3—10 days of fever with subsequent a febrile periods of 3—10 days [31,40]. It is thought to be a typical but rare manifestation of Hodgkin's lymphoma [40].

Remittent fever is defined as fever with daily fluctuations exceeding 2 °C but at no time touches normal [38]. Remittent fevers are often associated with infectious diseases such as infective endocarditis, rickettsiae infections, brucellosis, among others [31]. Relapsing fevers refer to those that are recurring and separated by periods with low-grade fever or no fever [40,41]. Periodic or relapsing fevers are seen in malaria, lymphoma, borrelia, cyclic neutropenia, and rat-bite fever [40,41]. Fever associated with night sweats has been described in infectious diseases such as TB, Nocardia, brucellosis, liver or lung abscess and sub-acute infective endocarditis, as well as in non-infectious diseases such as polyarteritis nodosa and cancers such as lymphomas [42].

## Mechanisms underlying fever patterns

The mechanisms underlying the specificity of the fever patterns to certain diseases are not

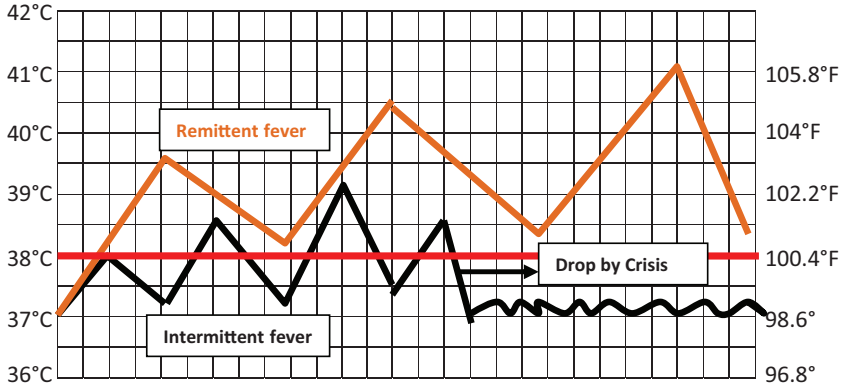


**Figure 3** Intermittent and remittent fevers. *Legend*: Intermittent fevers, for instance due to malaria, are present only for several hours during the day. Effective anti-malarial therapy leads to a rapid fever defervescence-by crisis. Remittent fever are characterised by daily fluctuations of fever exceeding 2 °C, but fever at no time touches normal.

completely understood. For some infectious diseases it may be related to the life cycle of causative agent. For instance, in malaria, parasites are released into the circulation after 48—72 h of erythrocytic cycle of plasmodium falciparum/ovale/vivax. Released parasites activate pyrogenic cytokines which then lead to cycles of fever every 48—72 h (tertian fever) [43]. However, plasmodium falciparum in contrast to other species may infect multiple red cells in a non-selective manner with each having independent erythrocytic parasite life cycles [43]. Consequently, fever due to this parasite is often quotidian (daily fevers spikes) [41]. Plasmodium vivax/ovale and *P. malariae* infects young and senescent erythrocytes that rupture to release merozoites (pyrogens) 72- and 96-h respectively. These events partly account for the cyclical nature of fever in these malarial fevers.

A down regulation of cytokine release after repeated exposure to pyrogens such as LPS may lead to fever remittance or intermittence [44]. Recurrent fevers may be due to partial treatment of deep seated infections like abscesses or due to recurrent exposure to new antigens (e.g. allergens in hypersensitivity pnuemonitis) [45]. Such drug (allergens) may manifest with eosinophilia in patients with drug fever. In cyclic neutropenic fevers, febrile episodes correspond to periods of neutropenia and are due to repeated bacterial infections [46]. In cancers and pulmonary embolism, fever recurrence has been attributed, partly, to tissue necrosis as phagocytosis of necrotic tissue leads to intermittent release of pyrogenic cytokines [45].

Recurrent fevers may be related to the pathogenesis of the disease as exemplified in relapsing fevers due to spirochetes where episodic spirochetemia lead to episodes of fever accompanied by fever free periods which coincides with disappearance of spirochetes from the circulation [47]. Night sweats are common in healthy adults but they become clinically significant if associated with fever and drenching [42]. They may be attributed to pyrogenic properties of certain diseases which result in early morning fever spikes accompanied hours later by fever remission presenting as night sweats [42].

### Significance of fever patterns

In clinical practice, many typical fever patterns described above are rarely observed. This is as a result of several confounding factors such as ingestion of antipyretics, partial treatment infectious disease-related fevers with antimicrobials and failure to mount fever in the face active infection (for instance the elderly, immunocompromised and severely malnourished individuals may not mount fever [13]). Furthermore, the occurrence of concurrent infections by multiple agents in an individual may alter typical fever patterns associated with specific infectious diseases. For these reasons, the utility of fever patterns in clinical diagnosis is often limited [48].

However, when observed, typical fever patterns may provide some useful diagnostic clues for infectious diseases without localising signs such as malaria and typhoid. They may also prove useful in eliminating unlikely diagnosis while directing possible diagnostic investigations to be undertaken for confirmation. In poor resource settings, analysis of fever patterns may provide diagnostic clues for difficult to diagnose infectious diseases especially when appropriate diagnostic investigations are unavailable or unhelpful. In the evaluation of pyrexia of unknown origin (PUO) for instance, the presence of low grade intermittent fever and night sweats without localising sign is a useful clue to investigate for extrapulmonary tuberculosis or to initiate empirical anti-tuberculosis therapy in tuberculosis endemic regions.

The nature of fever defervescence may also provide some diagnostic clues. For instance, in differentiating malaria from typhoid fever, effective anti-malarial therapy leads to fever defervescence by crisis (within hours) whereas in typhoid fevers resolution occurs by lysis (gradually over days) following effective antibiotics [39,43] (see Figs. 2 and 3). However, failure of fever to resolve by crisis does not exclude pre-existing malaria as malaria and typhoid fever may occur concurrently, especially in the tropics [49]. It has been suggested that fevers due to cancers can be distinguished from those due infectious diseases using the Naprosyn test [50]. When Naprosyn (Naproxen 375 mg twice daily), or other NSAIDS [51], is given for 3 days, fevers due to cancers display a rapid and sustained decline while little or no change is observed in fevers due to infectious diseases. However, Naprosyn test is unhelpful in differentiating neoplastic from noninfectious disorders such as connective tissue diseases [41]. Similarly, elevated serum procalcitonin level has been used to differentiate infectious from non-infectious causes of fever with variable results [52,53].

## Diseases called 'fever'

Based on its fundamental role in explaining the manifestations of diseases as well as its prominence as a feature of many diseases of man and

**Table 2** Fever in the appellation of human diseases: examples of diseases, brief features and origin of nomenclature.

| Disease | Brief overview | Origin of name |
|---|---|---|
| African tick-bite fever | A rickettsiosis caused by *Rickettsia africae* transmitted by cattle ticks of the *Amblyomma* genus. Manifests as an acute, febrile, and influenzalike illness, frequently accompanied by severe headache, prominent neck muscle myalgia, inoculation eschars and regional lymphadenitis. | Highly prevalent in Africa and often affects visitors to this region. |
| Argentine haemorrhagic fever | A viral illness caused by the Junin arenavirus. characterised by mucocutaneous hemorrhage and fever. | First discovered in Argentina. |
| Assam fever | Another name for visceral leishmaniasis; also called dumdum fever, black fever or kala-azar. | Assam is a state in northeastern India where an epidemic occurred in the 1880s and 1890s. Called black fever because of characteristics darkened skin; dum dum is an area close to Calcutta where the disease is also endemic. |
| Blue fever | Informal name for Rocky Mountain spotted fever, a rickettsial infection. | So named for the dark cyanotic discoloration of the skin after the initial rickettsial infection. |
| Beaver fever | Another name for Giardiasis; a parasitic disease characterised by chronic diarrhoea. | So named because of campers got the disease from drinking contaminated water that was inhabited by beavers. |
| Black water fever | A complication of falciparum malaria characterised by intravascular haemolysis, haemoglobinuria and kidney failure. | So named because of passage of urine that is black or dark red in colour. |
| Boutonneuse fever | Also called Mediterranean spotted fever, or Marseilles fever — due to a *Rickettsia* infection. | The French word boutonneuse means spotty. So named because disease is characterised by spots of widespread rash — an exanthema. |
| Brazilian pupuric fever | An illness of children caused by the bacterium *Haemophilus influenzae* biogroup aegyptius which causes fulminant sepsis. | It is mainly known from Brazil but there have been recorded cases in Australia. |
| Bullis fever syndrome | A disease transmitted through tick bites (*Ambylomma americanum*). Symptoms include fever, rash and headache. | The disease was first observed in soldiers training at Camp Bullis in America. |
| Bolivian hemorrhagic fever | An arenavirus infection similar to Argentine HF. | Endemic to the grain-producing province of Beni in Amazonian Bolivia. |
| Cat scratch fever | Febrile multi-systemic disease due to an intracellular bacterium named *Bartonella* spp. | Infection acquired from a scratch or bite from a cat. |
| Central fever | Also called hypothamic fever — sustained fever resulting from damage to the thermoregulatory centers of the hypothalamus. | |
| Cotton fever | A syndrome that is often associated with intravenous drug use, specifically the use of cotton to filter drugs like heroin. The cause of the condition is believed to be endotoxin shed by the bacteria *Enterobacter agglomerans* which colonizes cotton plants. | Described in the 18th century among cotton-mill workers. |
| Charcot's fever | A syndrome characterised by recurrent chills and fever, jaundice, and abdominal pain in the right upper quadrant that occurs with inflammation of the bile ducts due to intermittent impaction of a stone in the ducts. | Named after French physician, Jean-Martin Charcot, who described it. |

Table 2 (*Continued*)

| Disease | Brief overview | Origin of name |
|---|---|---|
| Canicola fever | A disease of humans caused by the canicola serovar of *Leptospira interrogans* and transmitted by infective urine, usually from dogs but rarely from cattle and swine. | Named canicola because of vector-dog (canine). |
| Colorado tick fever | Also called Mountain tick fever — an acute viral infection transmitted from the bite of an infected wood tick *Dermacentor anderson* | The disease is found almost exclusively in the western United States and Canada, mostly in high mountain areas such as Colorado and Idaho. |
| Chikungunya fever | Viral illness spread by the bite of Aedes mosquitoes; characterised by severe, sometimes persistent, joint pain as well as fever and rash. | In Swahili (an African language), Chikungunya means that which contorts or bends up — referring to the contorted (or stooped) posture of patients who are afflicted with the severe joint pain. |
| Crimean-Congo hemorrhagic fever | A hemorrhagic fever caused by the Crimean-Congo hemorrhagic fever virus, transmitted by ticks and by contact with blood, secretions, or fluids from infected animals or humans; characterised by fever, flu-like symptoms and haemorrhagic tendencies. | It occurs in the Crimea (Ukraine), Central Asia, and regions of Africa. |
| Dehydration fever | An increase in temperature in a neonate due to inadequate fluid intake, most severe in high ambient temperatures or when the infant is over-clothed. | Related to dehydration. |
| Dengue fever | Also called break bone fever — caused by dengue virus and characterised by fever myalgia and arthralgia and bone pains. | Origins of the word dengue not clear — some believe that it is derived from the Swahili phrase ''Ka-dinga pepo'', meaning ''cramp-like seizure caused by an evil spirit''. The Swahili word ''dinga'' may possibly have its origin in the Spanish word ''dengue'' meaning fastidious or careful, which would describe the gait of a person suffering the bone pain due to dengue virus. |
| Drug fever | The febrile response to a drug without cutaneous manifestations. Caused by a variety of drugs but most commonly beta-lactam antibiotics, procainamide, isoniazid, alpha-methyldopa and quinidine, among others. | Related to drug ingestion. |
| Ebola haemorrhagic fever | A viral haemorrhagic fever caused by the Ebola virus. Characterised by rapid onset of fever, malaise, muscle pain, headache, and pharyngitis, followed later by vomiting, bloody diarrhoea and maculopapular rash with bleeding at needle sites and bodily orifices. | Named after the Ebola River Valley in the Democratic Republic of the Congo (formerly Zaire), which is near the site of the first recognised outbreak in 1976 at a mission hospital. |
| Enteric fever | Fevers due to typhoid or paratyphoid fever. | So named because of prominent intestinal symptoms. |
| Fever blister | A cold sore around the mouth or nasal mucous membranes caused by herpesvirus 1. | Generally appears following a febrile episode or cold. |
| Febrile convulsions | A generalized tonic-clonic — grand mal seizure seen in infants to toddlers | Often due to rapidly rising fevers lasting from seconds to minutes; most are idiopathic |

Table 2 (*Continued*)

| Disease | Brief overview | Origin of name |
|---|---|---|
| Familial Hibernian fever | Also known as TNF receptor associated periodic fever syndrome, TRAPS-characterised by episodic symptoms such as recurrent high fevers, rash, abdominal pain, joint/muscle aches and puffy eyes due to mutations in a receptor for the molecule tumour necrosis factor (TNF) that is inheritable in an autosomal dominant manner. | 'TRAPS' was first described in 1982 in a boy of Scottish-Irish origin. 'Hibernia' is the Irish word for Ireland. |
| Familial Mediterranean fever | A hereditary autoinflammatory autosomal recessive disorder characterised by recurrent bouts of fever and peritonitis, sometimes with pleuritis, skin lesions and arthritis. | People with genetic origins in the Mediterranean basin are most commonly affected. Up to 50% of patients have a family history of the disorder, usually involving siblings. |
| Fort Bragg fever | A mild form of anicteric leptospirosis caused by *Leptospira autumnalis*, more common in children, and characterised by an abrupt 'toxic' state, with fever, shaking chills, headache, etc. | First observed among military personnel at Fort Bragg, North Carolina. |
| Fever of unknown origin (FUO) | Classical FUO is defined as (1) a temperature greater than 38.3 °C (101 °F) on several occasions, (2) more than 2 weeks' duration of illness, and (3) failure to reach a diagnosis despite 3 days of inpatient investigation or >2 days out-patient visits | Also known as pyrexia of unknown origin (PUO) —no known aetiology |
| Glandular fever | Viral infection caused by the Epstein-Barr virus presenting as fever, sore throat, swollen lymph nodes and lethargy. | So named because of effects on glands (lymph nodes). |
| Fictitious fever | Elevated body temperature falsely induced by either manipulation of the thermometer or self-injection of contaminated material. Common in young women, especially in those who are frequently allied with health professions. | So named because fever is falsely induced. |
| Hay fever | Also known as Allergic rhinitis — an allergic inflammation of nasal airways due to exposure to allergen from pollen or dust. Rose fever is a form of hay fever caused by grass pollens released while roses or other flowers are blooming. | Hay is the allergen — i.e. grass, legumes or other herbaceous plants that have been cut, dried, and stored for use as animal feed. |
| Haverhill fever | The bacillary form of rat-bite fevers, due to *Streptobacillus moniliformis*, and transmitted through contaminated raw milk and its products. Characterised by moderate fever, joint pain, and a diffuse red rash, located mostly on the hands and feet | It was first described in Haverhill, Massachusetts United States, in 1926. |
| Humidifier fever | Fever following exposure to amoebae, bacteria, and fungi found in humidifier reservoirs, air conditioners and aquaria. | Acquired from humidifiers. |
| Izumi fever | A form of Pseudotuberculosis caused by *Yersinia pseudotuberculosis*. First described as a scarlet fever-like febrile disease in Japan in 1929. | Named after the discoverer. |
| Jaccoud's dissociated fever | A form of febrile meningitic fever accompanied by a paradoxical slow and irregular pulse rate, seen in patients with tuberculous meningitis. | Named after Sigismond Jaccoud, a Swiss physician (1830—1913), who described it. |

Table 2 (*Continued*)

| Disease | Brief overview | Origin of name |
|---|---|---|
| Jamshedpur fever | A historical febrile disease of children characterised by sudden onset fever, vomiting, diarrhoea, convulsions, drowsiness, hypoglycaemia, high mortality and fatty changes on liver necropsy. Now believed to be Reye's syndrome because of close similarities in clinical presentation. | So named because it caused a mysterious fatal epidemic in 1954 in the town of Jamshedpur in Bihar, India. |
| Katayama fever | Acute schistosomiasis — seen after acute infection with *S. mansoni* or *Japonicum*; characterised by fever, urticarial rash, bronchospasm and hepatosplenomegaly due to immune complex formation. | Katayama is a town in Japan where the disease is endemic. |
| Lassa fever | An acute viral hemorrhagic fever due to the *Lassa* virus | First described in 1969 in the town of Lassa, in Borno State, Nigeria. |
| Metal fume fever | Also known as Monday morning fever — an illness caused primarily by exposure to certain fumes. Workers breathe in fumes from chemicals such as zinc oxide (ZnO) or magnesium oxide (MgO), which are themselves created by heating or welding certain metals, particularly galvanized steel. | Named derived from exposure to metal fumes. |
| Omsk Hemorrhagic fever is the virus | Caused by the *Omsk* Hemorrhagic Fever Virus (OHFV), a member of the Flavivirus family. | Virus was discovered after a outbreak between 1945 and 1947 in Omsk, Russia. |
| O'nyong-nyong fever | A togavirus infection transmitted by bites from anopheline mosquitoes; characterised by polyarthritis, rash and fever. | The name comes from the Nilotic language of Uganda and Sudan and means ''weakening of the joints''. |
| Oroya fever | Acute bartonellosis; Also known as Carrion's disease — due to bacterium *Bartonella bacilliformis*; characterised by fever and anaemia. | Oroya is city in Peru where the 1st outbreak occurred in 1875. |
| Pappataci fever | Also known as Phlebotomus fever or sandfly fever — a vector-borne febrile arboviral infection caused by three serotypes of Phlebovirus (sandfly). | Name 'Pappataci', comes from the Italian word for sandfly. |
| Paratyphoid fever | Infectious disease similar to typhoid, though usually milder, caused by any of several organisms: *Salmonella paratyphi* (paratyphoid A), *S. schottmulleri* (paratyphoid B), or *S. hirschfeldii* (paratyphoid C). | So named because of similarity with typhoid fever. |
| Parrot fever | Also known as Psittacosis — caused *Chlamydophila psittaci* infects birds and sometimes human. Severe atypical pneumonia most prominent manifestation in humans. | Contracted from parrots, pigeons, sparrows, hens, ducks. |
| Pontiac fever | A nonpneumonic variant of *Legionella* infection | Named after an outbreak in Pontiac, Michigan, in 1968. |
| Puerperal fever | Also called childbed fever; presents as fever during or shortly after childbirth, miscarriage or abortion. | Named derived from the Latin puer, male child (boy), purperium is the period following delivery. |
| 'Q' fever | Caused by bacterium *Coxiella burnetii*; most common manifestations are flu-like symptoms, fever, malaise, headache myalgia, and joint pains. | Q stands for query — 'Q' was used because causative agent was unknown at time of first outbreak. |

Table 2 (*Continued*)

| Disease | Brief overview | Origin of name |
|---|---|---|
| Rabbit fever | Also known as Tularemia — potentially fatal infectious disease of animals and man caused by the bacterium *Francisella tularensis*. | Discovered in 1911 during an outbreak of rabbit fever, when the disease killed a large number of ground squirrels in the area of Tulare Lake in California |
| Rat bite fever | Febrile human illness caused by two types of anaerobic bacteria transmitted by rodents, rats in most cases, which is passed from rodent to human via the rodent's urine or mucous secretions. | The majority of cases are due to the animal's bite |
| Relapsing fever | Caused by certain bacteria in the genus *Borrelia*, transmitted through the bites of lice or soft-bodied ticks., characterised by sudden fever, chills and joint pains. | So named because of characteristics relapsing febrile episodes — fever that persist for 2—9 days, and then disappear to recur. |
| Rheumatic fever | An inflammatory disease characterised by fever, joints pains and swellings due to Group A streptococcal infection. | Similar in presentation to rheumatism. |
| Rift valley fever | Viral zoonosis of animals and man spread by mosquitoes and caused by rift valley virus a member of the Phlebovirus genus — Bunyaviridae family. | The virus was first identified in 1931 during an investigation into an epidemic among sheep on a farm in the Rift Valley of Kenya. |
| Ross river fever | Mosquito-borne infectious disease caused by infection with the Ross River virus: characterised by influenza-like illness and polyarthritis. | So named because virus was 1st isolated in 1959 from a mosquito trapped along the Ross river, in Townsville, Queensland, Australia |
| Scarlet fever | Characterised by fever and a red coloured rash due to exotoxin released by *streptococcus pyogenes*. | Named derived from characteristic scarlet-like rash — bright red colour rash. |
| Sennetsu fever | Caused by a bacterium named *Neorickettsia sennetsu* and transmitted by the ingestion of infected trematodes in raw fish. Characterised by sudden high fever, headache, muscle aches, nausea and vomiting. | Named derived from causative organism. |
| Spotted fevers | Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*, a species of bacterium that is spread to humans by Dermacentor ticks. Initial signs and symptoms of the disease include sudden onset of fever, headache, and muscle pain, followed by development of rash. | The name ''Rocky Mountain spotted fever'' is considered a misnomer as after 1930 when it was first recognised in mountainous areas of the USA, the disease has occurred in many areas of the United States other than the Rocky Mountain region. |
| Trench fever | Also called five day fever-because of characteristic relapsing five day fevers. It is caused by *Bartonella quintana* and transmitted by body lice. Also called quintan fever, shin bone fever, tibialgic fever; characterised by high fever and headache, associated with back pain and leg pain and a fleeting rash. | So named because it was first observed in the trenches of the western front of the world war 1 due to poor hygiene and sanitary condition. |
| Tsutsugamushi fever | Also known as Scrub typhus. Caused by a bacterium named *Orientia tsutsugamushi*. Wild rodents and occasionally dogs may be hosts from where it can be carried to humans by infected mites. | The name Tsutsugamushi is derived from two Japanese words: 'tsutsuga', meaning something small and dangerous, and 'mushi', meaning creature. The infection is called scrub typhus because it generally occurs after exposure to areas with secondary (scrub) vegetation. |
| Typhoid fever | Also known as typhoid — a common worldwide illness, transmitted by the ingestion of food or water contaminated with the feces of an infected person which contain the bacterium *Salmonella typhi*. | The name of ''typhoid'' was given by Louis in 1829, as a derivative from typhus. |

Table 2 (*Continued*)

| Disease | Brief overview | Origin of name |
|---|---|---|
| Typhus fever | Any of a group of related diseases caused by various species of *rickettsia* that release toxins into the blood. The bacteria are transmitted by lice, fleas, mites, and ticks. Characterised by headache, chills, fever, depression, delirium and general pains and the eruption of red rashes on the skin. | . The name comes from the Greek typhos (τῦφος) meaning smoky or hazy, describing the state of mind of those affected with typhus. |
| Undulant fever | Another named for brucellosis. Also called Malta fever. Caused by intracellular bacterium *brucella* spp. A multi-systemic disease with protean manifestations. | So named because of wave-like or undulant nature of febrile response. Named Malta fever because it first discovered in Malta during the Crimean war in the 1850s. |
| Uveoparotid fever | A form of Sarcoidosis characterised by low grade fever, anterior uveitis and chronic parotid swelling. Also called Heerfordt's disease. | Named derived from symptoms. |
| Valley fever | Also known as Coccidioidomycosis — a disease caused by fungi — *Coccidioides immitis* and C. *posadasii* species; present with either no symptoms or mild symptoms in immunocompetent individuals. May disseminate to affect lung, skin, brain, skeleton and other body areas. | So named because of outbreaks in endemic regions such as San Joaquin Valley or Bakersfield, California, and Tucson, Arizona, or parts of southern New Mexico or west Texas. |
| West Nile fever | First clinical phase of infection by West Nile virus transmitted by mosquitoes; infects birds, man and other animals. Characterised by fever, headache and lymphadenopathy. | First isolated from a feverish 37 year old woman at Omogo in the West Nile District of Uganda in 1937 during research on yellow fever virus. |
| Yellow fever | A viral haemorrhagic fever caused by the yellow fever virus and transmitted by bite of female mosquitoes. Characterised by fever, nausea, and in severe cases jaundice due to liver damage. | So named because characteristic symptom-jaundice or yellow eyes. |

Data from Refs. [50,51] and from Wikipedia free encyclopaedia.

animals, fever is often included in the appellation of many diseases. Table 2 outlines diseases that have been called fever as well as the origins of their names. The naming of diseases called fever are usually based on specific epidemiological and clinical characteristics of the disease including: the way the disease is acquired (e.g. Hay fever is a febrile illness due to exposure to 'hay' in predisposed individuals); the transmitting vector/agent (e.g. cat scratch fever is an infectious disease due to a bite or 'scratch from a cat'); the prominent clinical manifestation (e.g. yellow fever is a viral illness so named because jaundice or 'yellow eyes' is a prominent manifestation in severe cases); the geographical location where the disease was first discovered (e.g. Lassa fever is a haemorrhagic viral infection so named because it was first described in 1969 in a village named Lassa, in Borno state, Nigeria [54]); where it is highly prevalent (e.g. Familial Mediterranean fever is a hereditary febrile disease common among people in the Mediterranean region); where a major outbreak occurred (e.g. Pontiac fever, a non-pneumonic variant of *Legionella* infection is named after an outbreak in Pontiac, Michigan, in 1968 [55]).

Some appellations are merely historical (e.g. Assam fever, another named for visceral leishmaniasis, was used to describe an epidemic of visceral leishmaniasis that occurred in Assam, a state in northeastern India in the 1880s and 1890s. This name is hardly used today), while some primeval names have remained unchanged till date —for instance the name typhoid fever was coined by French physician Pierre Louis in 1829 to distinguish the disease from typhus [56,57]. Another historical appellation is Jamshedpur fever, a rapidly fatal febrile disease which in 1954 caused an epidemic among children and young adults in the

town of Jamshedpur in Bihar, India [58]. Because of close similarities in clinical presentation, this fever is believed to have been Reye's syndrome [59].

## Concluding remarks

Fever is recognised an ancient adaptive compensatory defence mechanism leading to immune activation, decrease in bacterial and viral growth rate, and improve host survival in response to invasion by foreign antigens [60]. However, fever is not without its ill-effects, especially in cases of very high fevers, or when high fever is associated with co-morbidities such as severe sepsis, and pre-existing cardiopulmonary disease [60]. It has been suggested that fever is necessary for evolutionary survival of species by accelerating the recovery of infected individuals with localised or mild to moderately severe systemic infections while hastening the demise of hopelessly infected individuals, who pose a threat of epidemic disease to the species [60,61]. Therefore for some, fever may be a blessing, while for others a curse.

In view of its integral role in the pathogenesis of diseases, fever will remain a cardinal manifestation of old, new and emerging diseases, whether infectious and non-infectious disease. It is therefore imperative for scientist and clinicians alike to continue to harness and expand knowledge gained so far in the understanding of the febrile response in order to improve on the diagnosis, prevention and management of the numerous diseases characterised by fever.

## Funding

No funding sources.

## Competing interests

None declared.

## Ethical approval

Not required.

## Acknowledgment

I am grateful to Dr Abdulrazaq Habib, Chief Infectious Disease Unit, Aminu Kano University Teaching Hospital, Kano State, Nigeria, for reading through this paper and providing useful comments and suggestions.

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