Clinical Autonomic Research (2020) 30:317–323
https://doi.org/10.1007/s10286-020-00698-x

REVIEW ARTICLE

Sudor Anglicus: an epidemic targeting the autonomic nervous system

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Received: 12 May 2020 / Accepted: 15 May 2020 / Published online: 20 May 2020

Abstract
Renaissance England witnessed a series of brief epidemics of a rapid and often fatal illness, the predominant feature of which was a disturbance of the autonomic nervous system. Profuse sweating was both an emblematic and ominous sign of this *Sudor Anglicus*. Its story is medically fascinating as well as historically noteworthy. Possible sites of pathological involvement include the hypothalamus, serotonergic neurons in the brainstem or spinal cord, autonomic ganglia, peripheral sympathetic nerves, neuroeffector junctions, or eccrine glands. Of candidate etiologic agents, a virus is most likely, given the seasonal variation, geographic clustering, and pattern of spread of the epidemics. Hantaviruses, enteroviruses, influenza, and others provide clinical comparisons, but a definitive match with known viruses has remained elusive.

Keywords Hyperhidrosis · Sweating · History of medicine · Epidemics · Hyperthermia

Introduction

Five summer and fall outbreaks between the years 1485 and 1551 swept through England, spreading rapidly from town to town and disappearing within 1–2 weeks. Tens of thousands were left dead. Although the 1528 epidemic spread to the European continent, the locality of the majority of outbreaks corresponded in name with what became known as the English sweating sickness.

Historical relevance

The English sweating sickness emerged at a turning point in English history. The first reports came in the weeks preceding the battle of Bosworth Field on 22 August 1485, and "spread unusual terror" [43]. The sweating sickness fell upon London within 3 weeks of the entry of the army of Henry Tudor in 1485. His defeat of King Richard III at the battle of Bosworth Field marked the end of the War of the Roses and the beginning of the Tudor dynasty. The pageants that welcomed the new monarch were interrupted, and his coronation as Henry VII delayed, by the visitation of a disease which, according to John Caius, an eyewitness to the 1551 epidemic, "for its sudden sharpness and unwonted cruelty, surpassed the pestilence" [47]. Hall's Chronicle documented that in 1485, "a new kind of sickness came suddenly through the whole region even after the first entering of the king into this isle, which was so sore, so painful and sharp that the like was never heard of to any man's remembrance before that time. For suddenly a deadly and burning sweat invaded their bodies and vexed their blood with a most ardent heat...so that, of all of them that sickened, there was not one among a hundred that escaped" [47]. Communities were decimated, agriculture was interrupted, and many students and university faculty at Oxford and Cambridge died [16, 17].

The epidemic of 1528 interrupted Anne Boleyn's affair with King Henry VIII when she contracted the sweating sickness. According to the French ambassador Jean du Bellay, who himself survived the sickness, "As soon as he heard of her infection, Henry cast gallantry to the winds and fled from her side, keeping on the move for several weeks, dosing himself with numerous medicaments, hearing three Masses and confessing daily" [47]. Their separation occasioned a tender romantic correspondence as Henry VIII pursued his mistress Anne more intently. When Pope Clement VII refused Henry's request to annul his marriage to his wife, Catherine of Aragon, so that he would be free to marry

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Anne, Henry altered his strategy. Following a secret wedding in 1532, he and Anne were formally married 2 months later in 1533. The Archbishop of Canterbury Thomas Cranmer then declared Henry's marriage to Catherine null and void and his marriage to Anne valid. These events led to the Church of England breaking away from Rome. As Queen of England, Anne was unsuccessful in bearing a son, and as Henry turned his eyes to Jane Seymour, he had Anne investigated for high treason. Anne was arrested on false charges, imprisoned in the Tower of London, tried, convicted, and beheaded. Had Anne Boleyn not recovered, history might have turned out quite differently. In the words of one commentator, "Happy, indeed would it have been for the ill-fated Anne, had the dart penetrated more deeply" [43].

Following the final epidemic of 1551, the English sweating sickness has not been seen again. Its nature remains one of the unsolved mysteries in the history of medicine.

Clinical features

The sweating sickness affected people of all ages and social classes and often struck middle-aged persons who were previously in robust health [16]. Du Bellay observed that, "You have a slight pain in the head and at the heart; all at once you begin to sweat" [47]. Several contemporaneous clinical descriptions of the English sweating sickness [9, 21, 52] afford modern medical detectives an opportunity to conjecture what its etiology and pathogenesis might have been. The only surviving medical accounts of the period are from Thomas Forestier and John Caius. Forestier, an eyewitness to the 1485 epidemic, recorded that, "This sickness comes with great sweating and... with a redness of the face and all the body and a continual thirst, with a great heat and headache" [21].

John Caius, who was president of the Royal College of Physicians, was an eyewitness to the 1551 epidemic, on which he wrote a monograph documenting the following sequence of signs and symptoms:

> First by pain in the back, or shoulder, pain in the extreme parts, as arm, or leg, with a flushing or wind as it seemed to certain of the patients, fleeing the same. Secondly by the grief in the liver and nigh stomach. Thirdly, by pain in the head, and madness of the same. Fourthly by a passion of the heart…it lasted but one natural day [50].
>
> Suddenly these persons dripped with a great sweat without apparent reason, unaccustomed as they were to this disease. They first began to feel warm internally, after which they burned, the heat having spread already to the most extreme parts of their bodies. An enormous thirst developed and wild agitation. The disease attacked the heart, the liver, and the stomach. All this was followed by a heavy dull pain in the head, by insane raving and delirium, and after this langour and an unconquerable necessity for sleep. For the disease was as violent as the poison of noxious air, because the mind was seized with fury and overcome with turpor. Then came a violent death [43].

For some, death occurred within 4–12 h [16]. The estimated case fatality rate was 30–50% [16, 23]. Polydore Vergil, court historian to Henry VII, also drew attention to the early and abrupt onset of profuse sweating combined with subjective heat:

> Suddenly a fatal sweat attacked the body wracking it with pains in the head and stomach, moreover there was a terrific sensation of heat. Therefore the patients cast off the bed coverings from the beginning… stripped off their clothes [52].

The sweat of those affected was not only profuse but also malodorous beyond what was ordinarily encountered in the conditions of that era. Forrestier wrote, "And this sickness cometh with a grete swetyng and stynkyng" [16]. Witnesses described their sweat as foul or noisome [43].

Sweat alone was the secretion of copious quantity, and fulminant hyperhidrosis was followed by rapid death, typically within 24 h or less [6, 26, 42, 46, 47, 50, 56]. Sialorrhea was not a feature, as the lips and tongue appeared dry and parched [43]. Additional symptoms included headache, palpitations with a quivering and unequal pulse, dyspnea, thirst, flushing, chest and abdominal pain, and less frequently nausea, vomiting, or constipation [21, 43]. Absent were diarrhea, hemorrhage, or cutaneous hemorrhagic manifestations such as petechiae or ecchymoses [26, 43]. Among the possible mechanisms of death is hypovolemic shock secondary to the massive fluid loss from hyperhidrosis [48]. Hyperthermia, cardiac, or pulmonary failure cannot be excluded.

Physiology and localization

A pathologic process might interact with the autonomic nervous system at any of several levels to cause profuse sweating.

Brain

At the level of the central nervous system, the preoptic and anterior hypothalamic areas play a key role in temperature regulation. Elevation of core temperature induces a generalized thermoregulatory response as an efficient means of heat dissipation [14]. On rare occasions lesions of the hypothalamus may cause hyperthermia [11] but in general

do not present with hyperhidrosis [10, 29, 31]. Contemporaneous reports of the English sweating sickness describe a generalized pattern of profuse sweating, first appearing on the neck, face, and shoulders, then involving the whole body [43, 52]. Whether fever occurred cannot be established with certainty, as the sweating sickness predated Galileo's invention of the thermoscope in 1592, the first medical use of a thermometer by Santorio Santorio in 1612, and Gabriel Fahrenheit's invention of a standardized alcohol thermometer in 1709. Whereas fevers were well known at the time, clinical descriptions of the sweating sickness focused less on heat and more on sweating as the disease's most distinguishing symptom. In contrast to the usual sequence of a febrile illness, in which fever precedes the sweating that signals a break in fever, Forestier's description identifies sweating as an early feature of this disease. His elaboration suggests, further, that the amount of sweating was disproportionate to the elevation in body temperature: "The heat in the pestilent fever many times does not appear excessive to the doctor, nor the heat of the sweat itself particularly high" [21]. For these reasons, it may be concluded that the profuse sweating of the English sweating sickness was a primary manifestation of the illness rather than a secondary thermoregulatory response to a febrile illness.

Of the therapeutic interventions available in that era, one regrettable treatment that some practitioners applied to the sweating sickness was to intensify the sweating process by vigorous warming. The patient would be sequestered in a room with windows closed, covered with layers of bedclothes, and subjected to a blazing log fire [16, 17, 43, 47]. Such treatments may have contributed to the disastrously high mortality rate [43].

Physiologic sweating is also mediated by nonthermal factors, particularly exercise. Generalized sweating begins within a few seconds of dynamic exercise and independently of core or skin temperature [44]. Contemporary studies have shown that this sweating is not mediated by β-adrenergic receptor mechanisms, as the response is not blocked by propranolol [1]. Studies have shown that partial neuromuscular blockade with vecuronium or cisatracurium besylate, which increases the effort needed to achieve the same force during isometric handgrip exercise, results in increased skin sympathetic nerve activity and a greater rate of sweating as compared to controls, suggesting that central command initiates nonthermal sweating [45, 54]. The precise central pathways of nonthermal sweating remain unclear.

Hyperhidrosis accompanies other signs of increased sympathetic outflow, such as tachycardia, tachypnea, hypertension, flushing, and mydriasis, in the syndrome of paroxysmal sympathetic hyperactivity that occurs within 1 week of severe head trauma, subarachnoid or intracerebral hemorrhage, or acute hydrocephalus [37]. A similar constellation of sympathetic activity occurs in autonomic dysreflexia in patients with chronic spinal cord injuries above the T6 vertebral level T6 [7]. These sympathetic storms occur in brief paroxysms, unlike the continuous diaphoresis that characterized the English sweating sickness.

Descriptions of "pains in the head," "madness," an "unconquerable necessity for sleep," and the mind "seized with fury and overcome with turpor" [43, 50, 52] strongly suggest cerebral involvement, whether or not hypothalamic dysfunction or engagement of central command accounted for the sweating.

Brainstem and spinal cord

At the level of the brainstem and spinal cord, sudomotor pathways descend and exit the spinal cord at vertebral levels T3–L2 to supply all eccrine sweat glands [25]. These pathways are susceptible to serotonergic stimulation. For example, drug-induced serotonin syndrome presents with hyperhidrosis, hyperthermia, neuromuscular hyperactivity, myoclonus, hyperreflexia, elevated blood pressure, and altered mental status. Serotonin syndrome may occur after a dose increase of a serotonergic drug, after a second serotonergic drug is added, or from intoxication from 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy), amphetamines, or cocaine [27]. Ergot alkaloids, another cause of serotonin syndrome, bind to serotonin receptors in the dorsal horn of the spinal cord [19]; erogots will be discussed in more detail further in this review.

Adrenal medulla

Further down the neuraxis, catecholamine-producing tumors of chromaffin cells of the adrenal medulla (pheochromocytoma) also present with sweating along with hypertension, palpitations, and headaches [41]. Centrally mediated pseudopheochromocytoma presents similarly but without significant elevations in catecholamine or metanephrine levels [34]. As these syndromes are paroxysmal, rather than continuous, it is unlikely that the English sweating sickness was an adrenal medullary disorder.

Peripheral nerves

Many infectious diseases can cause peripheral neuropathies affecting preganglionic or postganglionic neurons, but when sudomotor outflow is impaired, neuropathies reduce, rather than increase, sweating. Proximal hyperhidrosis may occur with dying-back neuropathies that cause extensive distal anhidrosis, but this is typically a mild and chronic process [15]. Whereas compensatory hyperhidrosis can occur in skin areas adjacent to regions of sympathetic denervation [15], descriptions of the English sweating sickness do not mention regional anhidrosis.

Ion channels

Hyperhidrosis is also recognized as one of the diagnostic features of autoimmune channelopathies causing central or peripheral nerve hyperexcitability. A prominent example is Morvan syndrome, which is associated with contactin-associated protein-like 2 (CASPR2), leucine-rich glioma-inactivated (LGI1), and voltage-gated potassium channel autoantibodies, and presents with hyperhidrosis, neuromyotonia, and severe insomnia [4]. The dysautonomic manifestations are presumed to arise from thermoregulatory dysfunction of the hypothalamus or raphe nuclei, which are among the brain regions where CASPR2 antibodies bind [28]. Unlike these autoimmune syndromes, which affect individuals sporadically, the English sweating sickness affected substantial clusters of entire communities at once.

Eccrine glands

Modulation of sweating can occur also through a direct effect on the sweat glands or their neuroeffector junctions. Of the 2–5 million sweat glands covering the human body, 90% are eccrine glands, whereas 10% are apocrine glands located mainly in the axillae, mons pubis, areolae, and circumanal area [25]. At maximal efficiency, eccrine glands are capable of secreting up to 3 L of sweat per hour [13, 25]. The tubular epithelia of the eccrine gland consists of a secretory coil and a reabsorptive sweat duct opening to the skin surface. Secretory activity occurs primarily in the clear cell. The secretory coil is made of clear cells and myoepithelial cells, which are innervated by M3 acetylcholine receptors, and of dark cells, which are innervated by β_2 adrenergic receptors [13]. In addition to acetylcholine, eccrine gland chemical mediators also include norepinephrine, epinephrine, pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal peptide, and atrial natriuretic peptide [25].

Hyperhidrosis can occur from cholinergic drugs such as pilocarpine and bethanechol [13]. The profuse sweating in the English sweating sickness suggests that, if pathology was at the level of eccrine glands, it engaged clear cell Na–K-ATPase, as this is the driving force of sweat secretion [25], rather than effecting decreased reabsorption in the sweat duct. Additional channels that might have been involved include the Na–K-2Cl cotransporter, aquaporin 5 channel, or L-type calcium channel [25].

A further possibility is that the sweating sickness might have been a direct biochemical assault on eccrine gland neuroeffector junctions. Calcium-mediated synaptic exocytosis at the eccrine neuroeffector junction requires the bridging of syntaxin 1A and SNAP-25 (a 25-kDa synaptosomal-associated protein) on the plasma membrane with synaptobrevin 2 on the vesicular membrane to achieve membrane fusion and the release of acetylcholine [32]. Whereas botulinum toxins block this process, causing anhidrosis, perhaps an unknown toxin might upregulate it, driving hyperhidrosis. As proof of principle, cultured hippocampal neurons infected with recombinant Semliki Forest virus into which was inserted the whole open reading frame of SNAP-25 were made to greatly overexpress SNAP-25, causing a perturbation of synaptic function [39].

A potential gastrointestinal analogy to massive overstimulation of eccrine secretion is cholera.The cholera toxin is an oligomeric protein produced by *Vibrio cholerae* bacteria. The toxin binds to GM1 gangliosides on the surface of intestinal epithelial cells, which then take up the toxin by endocytosis. Once inside the epithelial cells, the toxin causes constitutive cAMP production, which in turn causes profuse secretion of water and electrolytes into the lumen of the small intestine, leading to rapid dehydration [38]. If a sudorific toxin was responsible for the sweating sickness, considering the rapid spread of the disease, a hematogenous route of entry to eccrine glands can be postulated.

Mast cells

Finally, hyperhidrosis can be a feature of mast cell degranulation, in which histamine release causes flushing, sweating, pruritis, angioedema, nasal congestion, diarrhea, wheezing, or anaphylaxis [51]. The hyperhidrosis that occurs in patients taking opioids may be mediated by μ-receptors or histamine release [13]. However, the sweating which occurs in known disorders of mast cell activation is less prominent than the other symptoms, making a mast cell disorder unlikely as a sole explanation for the sweating sickness.

Odor of the sweat

Witnesses commented that the sweating was not only profuse but also malodorous. Among the chemical components of sweat, two stand out as potential candidates. Ammonia (NH_3), a byproduct of nitrogen compound catabolism and the principal source of the pungent smell of stale urine, is excreted also in sweat and can generate a detectable odor in hyperammonemic patients. Ammonia in sweat is derived from plasma NH_3 through nonionic passive diffusion to acidic ductal sweat and trapping of its ionized form (NH_4) [2]. As the chief source of plasma NH_3 is the liver, the sweating sickness may have impaired hepatic function. Secondly, the sulfur-containing sudorific drugs given to stimulate further sweating in some of these patients might also explain the malodorous urine.

Potential etiologies

Various theories have been advanced in an effort to explain the English sweating sickness. Each has its strengths and weaknesses, but not one of these suggested etiologies is identical to that of any other disease known then or since.

Loathsome vapors

Contemporaneous clinical descriptions drew from medieval concepts of contagion. Forestier attributed the sickness to "ill-natured, fetid, corrupt, putrid, and loathsome vapors" [50]. Caius wrote of "euel mistes and exhalatios drawn out of the grounde" and "thimpure spirites" and "humores euel and maliciouse...in the bodye" [17]. These explanations, while of historical interest, predate the germ theory of disease and provide little insight into the scientific basis of the disease.

More recent reviews speculate that the epidemics were triggered by an infectious pathogen, most likely a virus, considering their seasonal occurrence, eruptive onset, ephemeral course, and geographical predilections.

Ergotism

Willan in 1808 attributed the sweating sickness to "some disease or depravation in wheat, or to some noxious vegetable growing with it in particular situations" [40]. His explicit comparison was to ergotism, sporadic outbreaks of which occurred east of the Rhine in Europe due to consumption of rye grain contaminated with the fungus *Claviceps purpurea*. The clinical features of ergotism, which were well known at the time, consist of muscle twitching, spasms, involuntary movements with contorted postures, altered mental status, hallucinations, sweating, hyperthermia, paresthesia, and gangrene [19]. Accounts of the sweating sickness did not include these distinguishing motor manifestations. Further, rye cultivation was less popular in England than on mainland Europe, and ergotism would have been expected to persist for the duration of that year's crop. For these reasons the ergotism theory can be dismissed [24, 42].

Anthrax

Pulmonary or inhalational anthrax from spores in wool or herd fields contaminated with the spores of *Bacillus anthracis* is another suggested etiology [36]. Symptoms consist of chest discomfort and dyspnea progressing to respiratory collapse from hemorrhagic mediastinitis and pulmonary edema, but sweating is not a notable manifestation. A flaw in this theory is that the sweating sickness occurred in the south of England, whereas sheep farming was practiced predominantly in the relatively unaffected north [23]. Anthrax can also be acquired from bovine reservoirs, but profuse sweating is not known to be a prominent feature in neuroanthrax cases.

Arbovirus

Noting the summer preponderance of outbreaks and preceding rainfall, a rodent reservoir and arthropod vector have been proposed [50, 55]. Of the arboviruses, most occur in tropical regions, but malaria was once endemic to marshy areas in the east of England, was known at the time, and likely would have been recognized [20, 22]. Its most deadly species, *Plasmodium falciparum*, causes a tertian fever with cyclical, not continuous sweating. Of interest, mast cell release of serotonin, a potential mediator of sweating, is a proposed mechanism of thrombocytopenia in dengue fever [35]. All things considered, an arbovirus etiology for the sweating sickness seems improbable in that no exanthematous or hemorrhagic signs were observed. Further, insect vectors are simply not as prevalent in England as in other parts of the world, and accounts of the sweating sickness do not mention any influx of novel insects [50].

Influenza

Influenza is an intriguing possibility in light of the history of encephalitis lethargica during the pandemic of 1918–1919 [26, 42]. The profound and varied neurologic manifestations in some cases involved the hypothalamus, and as many as 30% of cases had moderate to profuse sweating acutely [5, 18, 53]. In modern times, a case of hyperhidrosis as the only symptom of post-influenza diencephalitis has been described [3]. Whereas some have discounted the influenza theory on the basis that it was well known at the time and would have been recognized [23], influenza viruses are notorious for their rate of mutation and genetic reassortment from year to year, which can yield unexpected variations in its pathologic effects. Alongside these factors was the appearance of the sweating sickness earlier in the year than is typical for the seasonal incidence of influenza. Even when hypothalamic involvement was present, other features of encephalitis lethargica, such as parkinsonism, have predominated. In the balance, influenza is an improbable explanation for the sweating sickness.

Enterovirus

The list of suspects also includes the enteroviruses, which are highly infectious and transmitted rapidly by the fecal–oral route [26]. Widespread anhidrosis has been described among the neurologic complications of an outbreak of a polio-like

enterovirus [12], but hyperhidrosis is not a known manifestation of this family of single-stranded RNA viruses.

Bunyavirus

The latest sweating sickness theory implicates the hantaviruses, which are single-stranded RNA viruses of the family *Bunyaviridae* that asymptomatically infect rodents and are transmitted to humans by inhalation of aerosolized rodent urine or feces. Hantaviruses infect human vascular endothelial cells, causing extensive damage to capillaries, and clinical presentation includes hemorrhagic fever and rapid-onset pulmonary interstitial and alveolar edema [8, 33]. As with the analogy to diarrhea in cholera, the copious volumes of pulmonary edema and effusions in hantavirus pulmonary syndrome might be a clue to the mechanism of profuse sweating in the sweating sickness. In support of the hantavirus theory is Forestier's description of "panting of the breath" and "difficulty of breathing" [24, 49, 50]. However, sweating is not a prominent feature in hantavirus pulmonary syndrome, and prominent pulmonary involvement is not confirmed by other descriptions of the sweating sickness. These details fall short of making a strong case [6]. It seems plausible, however, that an ancester of contemporary hantaviruses might have been the sought-after culprit.

Sweating can be seen in Crimean–Congo hemorrhagic fever, which is caused by a nairovirus within the *Bunyaviridae* family transmitted by ticks or by exposure to body fluids of infected animals. Sweating, when present, is not as profuse as that described in the sweating sickness, and visible signs of bleeding, such as petechiae or epistaxis, are typically evident [30].

Conclusion

A viral etiologic agent seems the most likely cause of the epidemics of the English sweating sickness, although the available evidence is insufficient to identify the precise organism. In addition, toxic exposures cannot be fully excluded from the list of possible etiologies. While other epidemics have come and gone, the English sweating sickness has not recurred in modern times. If a choice were possible between, on the one hand, witnessing a return of the sweating sickness and the opportunity to identify and study its etiology or, on the other hand, having the causative agent remaining evermore extinct, harmless, and unknown to medical science, the latter is preferable.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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