The last century of symptom-oriented research in emergency presentations – have we made any progress?

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Summary

This review is dedicated to the last century of symptom-oriented research, taking three symptom complexes as typical examples of medical progress, and focusing on emergency presentations. Landmark publications in each area are discussed, with an attempt to focus on the methods used to achieve major breakthroughs. In abdominal pain, progress was achieved over a century ago by correlating symptoms and surgical pathology. Most diagnoses were made by using the clinical tools elaborated with careful observation and clinical examination. Together with the later reported outcomes, surgeons had an early and powerful tool for symptom-oriented research.

In dyspnoea, progress was achieved much later, as a universal definition had to be elaborated over decades by consolidating clinical research, predominantly symptom-pathology correlation, and experimental research, such as function testing and experiments with animals and humans. In nonspecific presentations in emergency situations, progress has been achieved only recently, most probably owing to the fact that elderly patients are presenting in steeply increasing numbers, and the hallmark of disease presentation in the elderly seems to be less specific symptoms and complaints. This may be caused by altered physiology, polymorbidity, polypharmacy and the multiple difficulties encountered when taking histories in the elderly.

Taken together, symptom-oriented research has been an important contributor to medical progress in the last century. Though it may be challenged by image- and laboratory-oriented research, it will remain part of patient-centred research because the epidemiology of symptoms, their clinical outcomes and their diagnostic importance according to severity will be the basis for the diagnostic process.

Key words: nonspecific disease presentation, symptom-oriented research, dyspnea, abdominal pain, elderly, geriatric emergency

An abbreviated history of symptom-oriented research

Although at the end of the 19th century symptom-oriented research was the engine driving advances in medical science, it was suffering from deficient funding and a lack of visibility at the end of the 20th century. Because insufficient investment in symptom-oriented research was sensed, the National Institutes of Health (NIH) started a grant programme for pain, nausea and dyspnoea research, and the US Congress announced the “decade of pain research” at the start of the 21st century [1].

Medicine has changed since Hippocrates and Galen founded symptom-oriented research, and their prime goal – doing what is best for the individual patient [2] – has evolved into the concept of doing what is best for a large number of patients, “evidence-based medicine”, by use of modern research methods and statistics [3, 4].

Observation of symptoms and evolving disease was a key component of slow, but definite progress (see table 1 below) until the late 19th century, when new technologies, such as bacterial cultures on the aqueous humour of an ox’s eye allowing proof of the “germ theory” of infectious disease [5], and led to a series of medical revolutions. Together with other breakthrough technologies at the turn of the 20th century, such as the detection of X-rays [6], new insights into the human body were achievable, and surgery of the abdominal organs was now state-of-the art in an emergency presentation of, for example, abdominal pain [7].

The approach to symptom-oriented research in the early 20th century was different from now, but the results were surprisingly similar. Publications were numerous, and a textbook editor of 1917 complained of “the overflow of publications in medical journals” [8]. Articles were generally authored by a single male investigator who described his personal experience, rated signs and symptoms subjectively, and added case reports to make his point [9, 10]. They emphasised observation and clinical examination, the differential diagnosis, and indications for, for example, abdominal surgery, which were similar to those of the present day, as exemplified in comprehensive textbooks [8, 11].

In this review, three very different complexes of symptoms, exemplifying the respective methods used for research in...
each complaint, will be highlighted, with a focus on emergency presentations. Although nonspecific complaints have drawn attention only recently [12], abdominal pain has led the way due to the symptom-pathology correlation in surgically treated patients that was recognised at the beginning of the 20th century [9], when the fastest advances in symptom-oriented research were made in this area. Thirty years later, immense pathophysiological challenges had to be faced before acute dyspnoea could be associated with the regulatory mechanisms of respiration and underlying diseases [13], and up to the 1960s no consensus was reached as to the universal definition of this complaint [14].

Symptoms, complaints and symptom-oriented research: in need of definitions

Symptoms may be established as medically legitimate where they can be isolated conceptually and, where possible, their parameters defined and displayed tangibly. Thus defined, symptoms may be targeted for treatment or, where treatment is not available, attention given to the activities of daily life they are seen to affect. Thus, symptoms are understood in terms of problems located within the individual [15]. Symptoms are initially presented by patients in narrative form, and can therefore be called “complaints”. Only when semistructured interviewing was introduced by Louis [16] (see also table 1), were symptoms systematically assessed. In this review, we therefore prefer the term “complaints” when referring to the patient’s own perception. The essential steps in the diagnostic process are the analysis of symptoms, clinical examination and clinical reasoning. This review is about the first step, as the analysis of symptoms is known to be the most important contributor to the diagnostic process [17–19]. Symptom-oriented research is based on the problems or complaints presented by the patients. It is therefore problem-oriented. It is diagnosis- or differential-diagnosis-centred, the methods usually being observational. The importance of symptom-oriented research is shown by the importance of the diagnostic process. Irrespective of the approach chosen – (a) hypothetico-deductive, involving several steps of problem definition and hypothesis generation, (b) pattern recognition, involving a mental library of signs and symptoms, or (c) scheme-inductive reasoning, involving an organised structure of knowledge usually in the form of inductive trees [20] – the recognition and interpretation of symptoms remains the first and crucial step in analytical medicine [21].

Furthermore, the epidemiology of symptoms is the basis for the determination of any pretest probability, health outcomes according to symptoms are of importance in emergency situations and severity assessments of symptoms may aid physicians in decision making. In table 1, different approaches to symptom-oriented research are shown. Outcomes could be determined only by autopsy before the 19th century, but heavily relied on clinical diagnoses in the last century. Advances in statistical methodology were important for improvements, but the assessment of symptoms has also changed: Although histories were reported as the original narrative of the patients until the 19th century, structuring was important to improve discrimination, and finally “descriptors” were predefined in order to optimise standardisation, the latest invention being verbal autopsies, in which machine-learning was shown to be superior to physicians in certain experiments for the first time in medical history [22].

Specific and nonspecific complaints in emergency presentations

Though never exactly defined, the concept of specific presentations or complaints encompasses the idea that cer-

Table 1: Approaches to symptom-oriented research.

<table>
<thead>
<tr>
<th>Researcher</th>
<th>Method</th>
<th>Outcome</th>
<th>Statistical method</th>
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<tr>
<td>Hippocrates</td>
<td>Observation of symptoms</td>
<td>Mortality</td>
<td>Descriptive</td>
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<td>(500 BC) [2]</td>
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<tr>
<td>Morgagni</td>
<td>History of symptoms, unstructured</td>
<td>Autopsy results</td>
<td>Comparative (old cases in the literature)</td>
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<td>(1761) [117]</td>
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<tr>
<td>Laennec</td>
<td>Signs and symptoms Auscultation</td>
<td>Pathological anatomy</td>
<td>Validation (clinical examination)</td>
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<tr>
<td>(1819) [118]</td>
<td></td>
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<tr>
<td>Louis</td>
<td>History of symptoms, structured</td>
<td>Autopsy</td>
<td>Correlation</td>
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<td>(1834) [16]</td>
<td></td>
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<tr>
<td>Elliot</td>
<td>Questionnaire, predefined “descriptors”</td>
<td>Clinical diagnosis</td>
<td>Cluster analysis</td>
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<td>(1991) [18]</td>
<td></td>
<td></td>
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<tr>
<td>Wang</td>
<td>Data extraction, 22 original articles</td>
<td>Clinical diagnosis</td>
<td>Meta-analysis (pooled sensitivities, likelihood ratios)</td>
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<tr>
<td>(2005) [119]</td>
<td></td>
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<tr>
<td>Flaxman</td>
<td>Verbal autopsy Analysis</td>
<td>Clinical diagnosis</td>
<td>Random Forest method (machine learning)</td>
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<td>(2011) [22]</td>
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Figure 1

Specific and nonspecific presenting symptoms.
tian symptoms are more or less “specific” to a small group of diseases; for example, dyspnoea presenting as an emergency is quite specific for severe pulmonary or cardiac diseases such as obstructive and infiltrative lung disease, pulmonary embolism and oedema, as well as myocardial infarction or heart failure [23, 24]. Most probably, over 90% of all emergency presentations with severe dyspnoea will be diagnosed within this group. Severe dyspnoea needing immediate acute care is so specific for these conditions that it can be readily differentiated using simple ultrasound protocols [24].

In acute abdominal pain, appendicitis, cholecystitis, perforated ulcers, diverticulitis and ileus may account for 90% of diagnoses made postoperatively. In children, over 90% of acute abdominal pain is caused by appendicitis and nonspecific pain [23], whereas in patients under 50 years of age, four underlying diagnoses, and in patients over 50 years of age, seven diagnoses, account for >80% of all presentations with “acute abdomen” [26]. Therefore, acute abdominal pain and dyspnoea are typical examples of “specific complaints” (figure 1).

In the last century, symptom-oriented research focused on a relatively small number of these specific complaints. Textbooks of medicine and surgery have no more than two dozen chapters on presenting symptoms, if they are symptom-oriented at all [27, 28]. On the other hand, it is perfectly clear that patients’ complaints extend over a much broader spectrum, may well be multiple and complex, and often do not fit into the relatively narrow concept of specific complaints. Though naturally limited, the concept of specific complaints has boosted advances in medicine for over a century. The limitation to a small number of specific symptoms, however, seems to be a recent phenomenon, considering the 2500-year history of symptom-oriented research. It can be hypothesised that the breakthrough in technology at the end of the 19th century has contributed to this development, because textbooks published before the detection of mycobacteria are much more detailed in the description of a variety of symptoms and their assumed origin [5]. Powell, for example, aimed at delineating the connection between the morbid anatomy and the clinical symptoms, and proposed six different diagnoses (alveolar phthisis, catarhhal pneumonia, fibroid phthisis, haemorrhagic phthisis, recurrent phthisis, and tubercular phthisis) for a condition later to be known as tuberculosis [29]. It can be concluded that a century ago there was less focus on the small set of specific symptoms driving symptom-oriented research today – a much broader variety of complaints and symptoms was acknowledged as the important basis of the diagnostic process in medicine.

Up to the 1970s, symptomatology was more widely accepted as a diagnostic and research basis [30], but has ever since lost ground. Though focusing on a reduced set of symptoms has contributed to the success of modern medicine, it is obvious that certain presentations may have been underestimated and, boosted by the fact that a nonspecific presentation is often a hallmark of disease in the elderly [31], were found to be of importance only recently when geriatric (emergency) medicine emerged [32–34]. In contrast to specific complaints, nonspecific complaints may be defined as all complaints that are not part of the set of specific complaints, because an active definition would require an almost endless enumeration of possible symptoms and complaints [34]. Typical examples are generalised weakness [35], non-injurious falls [36], gait disturbance [37] and tiredness [38].

These complaints have not been described in the text books of the last century’s and are still largely disregarded today, although various cohorts have shown prevalence between 5% and 21% [39, 40] in emergency populations in Europe [40]. Therefore, nonspecific complaints were chosen as an example of a late breakthrough, possibly because of a re-vival of symptom-oriented research at the end of the 20th century.

Taken together, abdominal pain, dyspnoea and nonspecific complaints are selected for their high prevalence in emergency presentations [34], as well as for the fact that for each complaint the advances were made using the typical and successful methods of the respective decades when breakthroughs were achieved (surgery for abdominal complaints, physiological tests for dyspnoea, and prospective cohorts for nonspecific complaints).

Abdominal pain with emergency presentation: leader in symptom-oriented research

Scientific knowledge has to be concentrated to the extreme – more than 400 reviews and 5000 articles under the title of “abdominal pain” have been published. However, only one practice guideline [41] for acute care physicians is retrievable, which suggests a certain lack of interest by the scientific community as compared with diagnosis-oriented guidelines, which are abundant.

At the end of the 19th century, symptom-oriented research [42] was, next to technology [6], the main driver of progress in medicine. The importance and influence of surgery around 1900 can hardly be overestimated and is demonstrated by a quote of Maylard in 1910: “previously, it was only through the accidental light thrown upon the subject by a necropsy that a certain symptom during life received its correct explanation after death...” [43]. To exemplify the state-of-the-art in abdominal pain, cases discussed over a century ago shed light on the differential indication for surgery. One argument was that “…the longer the symptoms have persisted the more uncertain is the effect of operative treatment ...; operations, on the other hand, performed within a reasonable time of the onset of the symptoms are ... always immediately successful” [7]. At the onset of the 20th century, the symptomatology was well known to surgeons: complaints, symptoms and physical signs were adequately described and weighed against each other, with emphasis on the nature of the pain, the rigidity of the abdominal wall, the facial expression of the patient, fever, pulse and vomiting [9].

In the 1920s, when antibacterial agents were not available (except for arsenic compounds used against syphilis) mortality rates of 4% to 7% were reported for complicated cases of the two most common emergency presentations of acute abdominal pain, namely appendicitis and cholecystitis [44].
This relatively low mortality demonstrates that physicians and surgeons had incorporated the knowledge gained from symptom-oriented research at the incipient 20th century. Most relevant details of the patient history and physical examination for the majoropathologies were known at the time. Clinical signs and symptoms of peptic ulcers, peritonitis, pancreatitis, appendicitis, cholecystitis, enteritis and ileus were described in detail in textbooks [8, 45], and surgeons published cases of rare entities, such as mesenteric vein thrombosis [9], that they had unsuccessfully operated on.

Still, a few presenting complaints turned out not to be specific, such as “classical ulcer-type postprandial symptoms” [46] that, by today’s knowledge, do not help to discriminate between functional dyspepsia and peptic ulcer [47]. However, a history of prompt and good symptomatic relief by a course of proton-pump inhibitors suggests an acid-related disorder [48].

What other progress have we made in the last hundred years in diagnosing abdominal pain? Although dyspepsia was similarly defined in 1917 [8], “new entities” emerged: the “irritable bowel syndrome” was a term first used in the 1950ies, whereas “nonulcer dyspepsia” appears to have come into vogue in the 1940s [49, 50] after case-series in which patients with typical ulcer symptoms were confirmed not to have a peptic ulcer crater. In 1943 Edwards and Copeman studied 436 patients using barium X-ray; 50% had no evidence of structural disease despite dyspeptic symptoms, arguably owing to the mediocre diagnostic accuracy of the diagnostic method chosen [49].

The condition now called “nonspecific abdominal pain” has become the most frequent “entity” for abdominal emergency presentations in patients younger than 50 years of age. It was first described in the 1970s [51], was also called “undiagnosed abdominal pain treated in hospital” [52] and showed an excellent prognosis in long-term follow-up [53]. An overlap of chronic abdominal pain, irritable bowel syndrome and nonspecific abdominal pain was later apparent – these entities seem more prevalent in younger females [54] and lower income classes [55], but no underlying anatomical pathology has been found. In past decades, research interest in functional bowel disease was enormous; certain publications were cited over a thousand times [56]. Surprisingly, only for the last decades was evidence produced that symptoms may vary widely depending on sex and age of the patient. The first systematic review on emergency presentation of abdominal pain in the elderly was published in 1994 and included approximately 42,000 patients [57]. De Dombal concluded that acute abdominal pain in the elderly patient presents a significant and challenging problem because diagnostic accuracy is lower, and mortality far higher, than in younger patients [57].

It has since become evident that emergency presentations of elderly patients with abdominal pain may greatly differ from presentations in younger patients. Elderly patients often present later in the course of disease and they have more nonspecific complaints. At the same time, a broader differential diagnosis has to be considered. A high number of comorbidities, polypharmacy, altered mental status and failure of care facilities to communicate the reason for transfer have been proposed as explanations for these difficulties [33, 34, 57]. These findings are not exclusive to abdominal pain, and will be discussed in the section about nonspecific presentation.

Still, it seems surprising that these facts materialised only, considering that for over a century great clinicians have made important contributions by meticulously observing patients and correlating their observations with the final diagnoses and pathologies. One of these clinicians was William Osler, who mastered narrow descriptions and concise characterisations of different types of abdominal pain. Upon reading this following account [58] – “… pain in the splenic region, tenderness on pressure and slight swelling of the organ. On several occasions I have heard a well-marked peritoneal friction rub…” – most physicians in later centuries would diagnose splenic infarction.

Taken together, in the area of abdominal pain presenting as emergency, the major advances in research were made at the beginning of the 20th century owing to the widespread use of abdominal surgery. Though technology has greatly improved since, morbidity and mortality have not dramatically changed, if patients in similar conditions are compared [44, 59]. In the last fifty years, break-through findings using the methodology of symptom-oriented research were rare with the exception of functional bowel disorders [60], and publications therefore focused on special populations, such as the pregnant [61], paediatric [62] and geriatric [57].

**Dyspnoea with emergency presentation: the prolonged search for a definition**

Going back to the 19th century, dyspnoea was depicted as a rather nonspecific complaint: “the number of diseased states capable of giving rise to dyspnoea is so great, and of such various and even opposite kinds, that not even the first step can be taken towards assessing the value of dyspnoea in any given case” [63]. However, the comparison of two common conditions, cardiac dyspnoea and asthmatic dyspnoea, in the same publication shows that observation of typical patients was the prime tool of symptom-oriented research in the 19th century. The ongoing controversy about bronchitis being a precursor of asthma was started in 1868, and the differential diagnosis of pulmonary oedema, asthma and emphysema was broadly discussed at that time [63].

As for abdominal pain, the literature of the incipient 20th century is full of case reports describing most of the common and many of the rare illnesses, but there was no attempt to perform prospective observational studies or experiments in order to understand the nature of dyspnoea and the pathophysiology of breathing; taking emphysema as an example, neither aetiology [64] nor pathophysiology [65] was really comprehended in the 1920s. A major role was attributed to humidity, and Switzerland was cited as a country where the incidence of emphysema was low due to dry and cold air [66].

Between the world-wars, two hypotheses were proposed to explain hypercapnia in emphysema: Scott [65] suggested that impaired ventilation is the result of chemical factors that influence the respiratory drive; Christie [67] proposed...
that ventilatory insufficiency is primarily the result of abnormal respiratory mechanics, and that the respiratory muscles are unable to perform the necessary work to provide adequate ventilation. These hypotheses, which were generated from observation of symptomatic patients, were later proven to be imprecise or wrong [68], but the methods, such as cardiac [69] and pulmonary function testing [70], used to correlate symptoms with physiology had to be refined first [71]. In the 1920s, several novelties need to be noted: the time of all-male science was over [72], inter-observer differences were acknowledged as a fact when taking a patient’s history, and experiments were now agreed to associate symptom and function [72]. It was also increasingly clear that acute dyspnoea was quite a specific complaint, as the majority of underlying conditions were now attributed to the heart, lungs and kidneys [73]. Furthermore, it was recognised that cardiac dyspnoea occurred in two different forms: the nightly paroxysms [73] of congestive heart failure, in severe forms associated with Cheyne-Stokes type respiration [74], and as an accompanying or presenting symptom in myocardial infarction [75]. In the 1930s, Conner may have been the first to publish an observational study on “coronary thrombosis” with a complete outcome for over 200 cases. Furthermore, he realised that the presentation was dependent on gender, and that dyspnoea was one of the features of myocardial infarction [75]. Due to a lack of immediate publication, the first (self-)catheterisation in 1929 [76] was not repeated until the 1940s, when Courmand and Richards used the Fick principle to measure cardiac output and showed in hundreds of subjects that the procedure was safe [77]. In the 1940s and 1950s, pulmonary and cardiac pathophysiology [78, 79] was explored using newer methods such as plethysmography [78] and cardiac catheterisation [76, 77]. However, the definition of dyspnoea (“dyspnoea occurs whenever the individual’s actual ventilation cannot easily be provided by his breathing capacity”) given by Richards and Courmand in 1941 [80] was still similar to Means’ and Meakins’ in the 1920s [81, 82] and very mechanistic, omitting, for example, the fact of psychogenic hyperventilation. Richards believed in symptom-oriented research and quoted Conner in a lecture on dyspnoea: “...new advances should support and add to our simpler forms of knowledge, rather than replace them; ... in the analysis and treatment of disease, laboratory findings, whatever their nature, should be our servants and not our masters” [83]. This picture of the “true clinician” who was convinced that symptom-orientation should always lead the way, in daily practice and in research, would soon fade, as technology advanced. In the 1950s, symptom-oriented research had definitely moved from a case-report and single author based approach to a cross-sectional, multi-observer and group-oriented approach, incorporating Cochrane’s landmark paper on interobserver variability [3], but there was still no universal definition of dyspnoea. Wright commenced his 1954 publication with the words “dyspnoea has no generally accepted meaning in the scientific literature” [84]. One of the first conferences on dyspnoea in 1966 attempted to gather all information from the different specialties involved in dyspnoea research [85]. In the 1980s, the respiratory drive was investigated in depth and dyspnoea was experimentally correlated with certain external stimuli [86]. In 1990, it was finally acknowledged that there is no unique peripheral site that mediates dyspnoea. Rather, receptors in the airways, diaphragm, and intercostal muscles, as well as the sense of respiratory effort, can all be involved [87]. The term “breathlessness” was reintroduced in order to discriminate the different sensations a volunteer or a patient can experience when challenged [88]. After a century of research it was time to go back to the roots and ask physicians for more clinical differentiation in patients suffering from dyspnoea. Unfortunately, the distinguishable sensations were not very specific to a single cause, and not many clinicians have heard about the language of dyspnoea [87, 89]. About 20 years ago, standardised diagnostic protocols were introduced and ever since, standards, pathways and algorithms have been published for work-up in the office [90, 91], in the emergency department [92] and even when giving advice by telephone [90]. Taken together, the fastest advances in research on dyspnoea were made in the middle of the 20th century owing to the incorporation of the findings by physiologists into clinical practice. While multiple causes underlie dyspnoea in a general population, it has turned out to be a specific symptom in an emergency presentation, as the bulk of the underlying disease is cardiorespiratory. For further reading see table 2.

Nonspecific complaints with emergency presentation: still in search of a definition

Generalised weakness, repeated noninjurious falls and functional impairment are typical complaints in an elderly population [31]. According to different cohorts, their prevalence in emergency presentations is up to 21% [40], and patients under 65 years are contributing to this increasingly recognised type of presentation [40]. The literature on nonspecific symptoms is scarce, possibly owing to a missing universal definition. Considering that this task has taken decades in specific complaints, the scientific discussion certainly needs more original data to be able to agree on a general definition of nonspecific complaints. The first publications on patients presenting with weakness, functional impairment or dizziness appeared in the late 1980s and 1990s [31, 32]. They described a geriatric population, without focusing on emergency presentations, but were not able to trigger symptom-oriented research in this area. Over a decade later, the first articles on the nonspecific type of presentation in emergency settings were published and demonstrated that in 42% of all presentations an underlying condition was found in the emergency department (ED) [40]. This was confirmed by a later study showing that 50% of older individuals without specific complaints suffered from an acute medical problem [12]. The population presenting with nonspecific complaints turned out to be a particularly high-risk group for adverse outcomes (e.g. functional decline, dependence and death) [93].
In the 1990s it was recognised that functional impairment was mostly caused by muscle weakness, and multiple studies measuring muscle function were published [94]. However, the distinction between the “frail elderly” and the “elderly with acute functional impairment” was not made until recently, when it became apparent that frailty is a geriatric syndrome needing assessment with the prerequisite of a stable situation and an adequate setting – all of which are lacking in acute care [95–98]. Generalised weakness is one of the most frequent presenting symptoms in emergency presentations [39]. In a recent report, it was responsible for 13% of all nontrauma admissions and was the single most frequent presenting symptom in this group, being caused by serious disease in the majority of cases [34]. This contrasts with the common assumption that nonspecific symptoms, such as weakness, tend to be benign. Physicians in acute care settings face a significant challenge when evaluating patients with nonspecific symptoms, owing to the broad spectrum of underlying disease. The diagnostic work-up is usually time-consuming and the possibility of acute morbidity such as pneumonia [99–104] is high. With increasing age, acute illness tends to present in a nonspecific manner [100–104]. It has been reported that even myocardial infarction can present with overwhelming weakness [105]. The clinical presentation of infection in the elderly, as another example, is often atypical or nonspecific and might even appear to be unrelated to the underlying condition [33, 106]. In elderly patients, the typical manifestations of infection, fever and leucocytosis may be absent or blunted in up to 30% of serious infections [107]. It is a well-accepted fact that elderly patients may present with atypical symptoms of urinary tract infection such as weakness and subtle mental status changes. In fact,

| Table 2: Interesting reading on dyspnoea research. |
|---------------------------------|---------------------------------|--------|----------------|
| Finding/highlight | Field of interest | Year | Publication |
| Noxious vapours exhaled by lung | Cardiovascular/pulmonary | 204 | Galen [120] |
| Oxygen needed for combustion | Pulmonary/metabolic | 1775 | Lavoiser [121] |
| Periodic breathing | Cardiac | 1818 | Cheyne [122] |
| Dyspnoea and haemoptysis | Cardiovascular/embolism | 1870 | Johnson [123] |
| Cheyne-Stokes and CO₂ | Cerebral | 1908 | Pembrey [124] |
| pH and dyspnoea | Metabolic | 1913 | Henderson [125] |
| Cardiac dyspnoea and lung function | Cardiac | 1916 | Peabody [126] |
| Definition of dyspnoea | Cardiac and pulmonary | 1929 | Means [52] |
| Dyspnoea as angina equivalent | Cardiac | 1930 | Conner [79] |
| Pulmonary insufficiency | Pulmonary | 1941 | Courmand [80] |
| Dyspnoea and cough rating | Epidemiology/statistics | 1951 | Cochrane [3] |
| Lung stretch and dyspnoea | Pulmonary | 1954 | Wright [54] |
| Definition of dyspnoea | Cardiac and pulmonary | 1966 | Howell [55] |
| Diagnostic approach | Cardiac and pulmonary | 1969 | Pratter [127] |
| Chemosensitivity in dyspnoea | Pulmonary/asthma | 1994 | Kikuchi [128] |
| Telephone triage in dyspnoea | Cardiac and pulmonary | 2003 | Zoorob [90] |
| Cerebral activation and dyspnoea | Cerebral | 2009 | Leupold [129] |

| Table 3: Current attempts to describe or define nonspecific complaints. |
|---------------------------------|----------------|---------------------------------|
| Nomenclature | Setting | Definition/description |
| Home care impossible [12] | ED | (1) When primary care or referring physicians explicitly noted on referral note that home care services and/or social and familial support were not able to support the patient at home anymore. (2) When the triage nurse could not identify any specific chief complaint except insufficient social, familial and/or nursing support. |
| Nonspecific complaints [34] | ED | All complaints that are not part of the set of specific complaints or signs, or where an initial working diagnosis cannot be definitively established. Prerequisite are vital signs within normal limits and a triage level indicating the need of more than 1 external resource |
| Unexplained symptoms [130] | GP | Those complaints for which a general practitioner, after clarifying the reason for encounter, taking history and performing physical examination, is unable to establish a diagnosis |
| General disability [39] | ED | A conscious patient’s own (or referring institution’s) experience of rapid decline of physical and/or mental condition but no signs or symptoms from a specific organ and no knowledge of ongoing fever. Corresponding ICD-codes: R69, R41.0, R63.0, R63.4, R64, R69 |
| Atypical symptoms and nonspecific functional decline [33] | General medicine university hospital, almost all admitted from ED | Atypical symptoms were defined as six syndromes (delirium, falls, immobility, incontinence, functional decline and breakdown of social supports) with the following criteria: Delirium was defined by the criteria of DSM-III-R.11. Falls were unintentional displacement to the ground occurring within 1 week before admission. Immobility was loss of ability to ambulate or transfer within 1 week before admission. Incontinence was a new onset of the inability to control urination or defecation within 1 week before admission. Nonspecific functional decline was a change in the ability to perform personal activities of daily living and/or instrumental activities of daily living within 1 week before admission. A breakdown in social supports was the inability of the premorbid supports to continue to provide adequate care for that patient. |
| Frailty [36] | Community-dwelling older adults | Frailty was defined as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity |
| No cardinal symptom [131] | ED | None of these symptoms: Chest pain, abdominal pain, dyspnoea, headache. |

ED = Emergency Department; GP = general practitioner
delirium and functional decline may be the first signs of bacteraemia in the elderly. Such “nonurinary” symptoms are more likely to occur in patients with comorbidities and/or dehydration [108]. Similarly, more than half of patients older than 70 years can have nonrespiratory symptoms as the presenting complaint for pneumonia, and over a third have no systemic signs of infection [109]. Furthermore, physiological changes and pharmacological factors may limit changes in vital signs in response to an acute disease such as pneumonia, limiting the ability of clinicians to rely on vital sign abnormalities to identify serious illness in the elderly [110].

Even after two decades of research, defining symptoms such as “not feeling well”, “feeling weak”, “being tired”, remains a challenge, but has been attempted in different ways (table 3). A framework has recently been proposed, including a working definition [34]: “all symptoms that are not part of the set of specific symptoms can be called non-specific”, as it has been shown that multiple diagnoses are responsible for this type of presentation. Even a fair-to-moderate pretest probability would have to include over a dozen entities in as many diagnostic groups. This “negative definition” has a major advantage: there is no “endless” list of complaints defining the presentation. The disadvantage is the extremely broad case-mix. Therefore, it remains to be shown that “non-specific” is a presentation with common underlying diseases and outcomes, irrespective of the type of complaint, such as “not feeling well”, “feeling weak”, “being tired” or “feeling dizzy”. To come forward with a universally accepted definition is a prerequisite for the management of the patient by the use of diagnostic protocols. These have been developed for a number of presenting chief complaints, such as acute chest pain, dyspnoea, or flank pain [34, 92], where the pretest probabilities in all conditions are known, and where management strategies have been tested [111–113]. Unfortunately, in nonspecific complaints uncertainty often accompanies the diagnostic process, which results in ineffective or suboptimal triage of these patients, delayed ED throughput, and inadequate patient disposition [34, 114]. These factors may contribute to the reported unfavourable outcomes [115, 116]. Next to a universal definition, risk stratification tools are needed to efficiently manage patients with nonspecific complaints.

Conclusion

Symptom-oriented research needs to be reinforced — not only because it has been among the major drivers of scientific medicine in the last century and before, but also because the clinical features of disease (i.e. complaints, history and clinical examination) often provide noteworthy information that cannot be replaced by imaging and laboratory testing. Additionally, a thorough assessment of symptoms is low-cost and high-value, considering the continuous shortening of physician-patient interactions, and could lead to elimination of superfluous testing. Symptom-oriented research is also of importance for the epidemiology of symptoms and their pathophysiology. Health outcomes, such as quality of life and mortality, need to be known on the basis of symptoms, as a sound diagnosis is not always available in emergency situations.

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Figures (large format)

Figure 1
Specific and nonspecific presenting symptoms.