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Editorial

Fatigue—an Orphan Topic in Patients with Cancer?

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WHILST RESEARCHERS first dealt with fatigue in the eighteenth century, little progress has been made since then concerning the conceptualisation of this prominent phenomenon in cancer patients. Causal relationships are still unclear and helplessness prevails, with fatigue forcing patients to withdraw from daily activities because they feel, as they say, 'dead tired'. Looking at the literature, a nihilistic attitude towards fatigue within the medical community must be assumed. In the last few years, predominantly women and mostly nurses and psychologists have shown a scientific interest in fatigue research and their key publications summarise the existing knowledge [1]. However, there is no question that this phenomenon needs an interdisciplinary approach and, therefore, Stone and associates in their review article in this issue of the *European Journal of Cancer* (pp. 1670–1676, [2]) are to be congratulated for their initiative in tackling the problem as physicians. Fatigue in the cancer patient population has even been described as a dose limiting factor for certain types of cancer therapy [3] and physicians, therefore, cannot remain sceptical when confronted with this devastating aspect of quality of life.

Firstly, we obviously have a linguistic problem in the European countries when we speak about fatigue. What does it really mean? The term fatigue does not even exist in the German, Italian, Swedish or other languages and there is no universal word to be shared in the scientific community. Whilst German speaking persons use the word tiredness for healthy and pathological tiredness, other cultures seem to differentiate between tiredness as a healthy state and fatigue as an unusual, extreme state of tiredness, leading to exhaustion. These differences reveal the complexity of the phenomenon, not only in the linguistic sense, but also in its cultural understanding, interpretation and definition. It is important to see that fatigue in health has been defined by theorists as a human mechanism to maintain health [4]. In nature the feeling of fatigue helps the body to find its balance between rest and activity. It can be called a life sustaining state, similar to other physiological needs, such as thirst. Therefore, we might be wrong in assuming that fatigue is something generally to be avoided. Fatigue research in the 1960s had the aim of evaluating productivity in industrial working populations

[5]. However, deviations from 'healthy' or 'normal' tiredness are not always easy to recognise. What is the difference between the feelings of fatigue in healthy individuals and diseased persons? What are the characteristics of fatigue in cancer patients? Only a few scientific attempts have been made to clarify these important questions [6, 7].

Stone and associates, in their article, give an overview of fatigue from definition, to measurement and treatment. They cite new scientific work which has gained insight into the experience of fatigue in cancer patients [7, 8]. Here, further literature is suggested which theoretically underpins concepts which might guide further research activities. The integrated model of fatigue in cancer, developed by Piper, has been one of the first to explain its multidimensional and complex nature, including biochemical, medical, behavioural, social and psychological influences [9]. The energy analysis model by Irvine explains the unique role of energy in relation to the development of fatigue in cancer and not only addresses energy transformation patterns but also resources and psychological and physical modifiers [10]. Nail and Winningham in their model stress the unique role of other symptoms of cancer and their influence in the context of fatigue development [1]. They explain that symptoms, for example, pain, nausea or immobility, might lead to inactivity, promoting the development of secondary fatigue, which could also explain its high prevalence. Recent research has identified fatigue components and also tentatively supported the hypotheses of secondary fatigue, describing a vicious circle, leading to an activity/rest imbalance: unusual tiredness (fatigue) leads to increased need for rest, leading to activity intolerance, to weakness, to reduced physical performance, which again leads to the beginning of the vicious circle with unusual tiredness [11]. A further, new fatigue theory explains its development in three steps of nociception, perception and expression, similar to that proposed for pain [12]. This multidimensional concept presents the expression of fatigue at the physical, affective and cognitive level and these types of manifestation are used as parameters to measure it [11].

Stone points out that there might be very complex, biochemical mechanisms involved in the development of fatigue in cancer patients and he divides them into physical and psychological correlates. Cachexia, weight loss and muscle abnormalities might all correlate with certain cytokines and their influence in causing fatigue has been suggested. This

hypothesis can be supported by the fact that these symptoms occur commonly in patients with advanced cancer. The correlation of fatigue with advanced stages of cancer has been documented [11]. However, cancer patients seem to be a very heterogeneous group and there is still a lack of knowledge concerning the correlation of fatigue with specific types of cancer. Evidence is growing, that patients with lung cancer experience higher fatigue levels than others, such as patients with breast cancer [11, 13]. It can be suggested that different types of cancer correlate with different types of cytokines. Paraneoplastic syndromes have been observed widely, especially in patients with lung cancer and this might be explained by specific cytokines as well as with endocrine abnormalities. The production of cytokines could be seen as an immunological response mechanism of the body against the tumour and fatigue might be a side-effect of these cytokines. The fact that as yet, it has been difficult to document the correlation of cytokines with fatigue levels could be explained by problems with laboratory techniques or by the use of invalid fatigue measurement instruments. The possible correlation of anaemia with fatigue has stirred up much controversy. Is there relevant meaning? Is it just one further unknown mechanism correlating with anaemia? Whilst clinical experience shows that patients can tolerate chronic, mild anaemia, without increased fatigue levels, blood transfusions in palliative patients have been documented to lead to a small improvement, such as a decrease in weakness [14].

The high prevalence of fatigue in cancer patients cannot be explained without mentioning the influence of cancer treatment. The shift in ranking regarding prevalence of symptoms in the past years has to do with new, partially more intensive treatment strategies, chemo-, immunotherapy, combined treatment strategies, high-dose therapy, setting the patients at risk of fatigue. However, treatment can also relieve fatigue if it is able to reduce tumour bulk, especially if an organ function, such as oxygen exchange in the lungs, can be ameliorated by the treatment. If patients without tumour bulk receive adjuvant treatment, fatigue might result as an additional distress caused by the treatment [15]. Although it is common to attribute fatigue to cancer treatment, little evidence exists to support this belief. The production of by-products of cell death, the elimination of waste products or the reaction of the body to necrotic tissue have been discussed. Specific toxicity on different body systems might explain a variety of causes. It becomes evident that causes of fatigue in these patients are very complex and that any scientific investigation has to pay attention to the many different confounding variables, such as stage, type of cancer, treatment, further non-cancer medication, symptoms, age, gender and many more. Lastly, the results of any fatigue research will depend on the validity and reliability of fatigue measurement tools.

In 1921 Muscio stated that "the term fatigue be absolutely banished from scientific discussion and consequently that attempts to obtain a fatigue test be abandoned" [16]. Meanwhile psychometric research has advanced and in the last four decades, researchers have again constructed fatigue measurement tools. Tiredness or fatigue has been integrated as an item in many quality of life measurement instruments and some have even integrated a subscale on fatigue [17, 18]. However, for the explicit measurement of fatigue in cancer patients, only few validated instruments are currently available and their content, reliability and validity need to be

known before they should be used. Stone and associates in their review present four measurement tools, two of which were not developed in cancer patients [5, 19]. These two and many more instruments were developed in healthy and non-cancer populations and used for all kinds of purpose, including research in cancer patients. As today we know more about the difference of fatigue between healthy and different illness populations [7, 8], we have to admit, that this may not be a valid practice. Very recent developments should now make it much easier to do fatigue research valid and reliably. The cancer specific Piper Fatigue Scale is now available even in a short version [20] and the Multidimensional Fatigue Inventory also is one of the few instruments which has been developed in cancer patients and was validated in Dutch and in English [21]. In addition, the 20-item Fatigue Assessment Questionnaire also is available and reflects experience of fatigue (validated in German). It was developed out of qualitative research and tested in cancer patients and healthy individuals [11]. These instruments all include measurement of intensity, distress and also quality of fatigue and, therefore, take account of its multidimensional concept. They might suit more or less for a specific purpose, according to the aim of measuring either the experience or the consequences of fatigue.

Valid instruments will now allow the measurement of treatment-induced fatigue and thus help to evaluate quality of life-threatening effects of therapies. It will also help to develop treatment options and influence fatigue management. Whilst it seems unrealistic and unwarranted to reduce curative treatment in order to prevent fatigue, there might be other situations in which fatigue management represents a real option. The old questions about the fatigue relieving effect of corticosteroids, progestational steroids, anabolic steroids and psychostimulants are discussed in Stone's review. The influence of vitamins or fluid intake, during a period of higher demand, described many times, seem interesting subjects to be scientifically investigated.

A nihilistic attitude is no longer acceptable when we know that fatigue can be prevented, at least to some extent, in certain circumstances. It has been shown that breast cancer patients with adjuvant radiotherapy, who exercised 5 times per week (a brisk 30 min walk), demonstrated significantly less fatigue than a control group [22]. This management strategy can be supported by the theory of the rest/activity imbalance, which could, due to physical and psychological burdens, lead to the vicious circle phenomenon. However, nurses and doctors will have to be very careful when proposing exercise to cancer patients, as it might be a completely inadequate strategy for those with advanced disease. Fatigue levels were shown to be significantly higher in patients with metastatic disease than in those with localised disease [11]. Muscle wasting occurring in the course of illness is thought to be responsible for fatigue because it requires patients to exert an unusually high amount of effort to generate contractile force and altered muscular metabolism might occur [23]. These patients might suffer from exercise and prefer to use rest as the only available defence against fatigue. Here, management strategies might be geared towards helping patients to live with a limited 'energy account' and to learn to accept frequent rest periods without feelings of guilt. No question this would involve caregivers helping patients to cope and providing emotional and physical support. Recent data suggest that there is a correlation of depression with fatigue in

advanced cancer patients [11], but there is also evidence that fatigue does not follow the same course as depression over time in patients in less advanced stages of cancer [24].

Stone and associates also mention the important role of information in this context. Information becomes part of psychological interventions because it is the uncertainty about unknown things which induces anxiety and fear. Patients, relatives and friends need to know about possible causes to prevent them believing that the patient wants to be inactive, but rather cannot be active. They might be advised in which situation activity can have a positive influence on well-being and how far it is advisable to keep up a reduced every day schedule. This requires physicians, nurses, physiotherapists and psychologists to be aware of this devastating symptom, be it in an adjuvant situation, where something can be done about it, or in an advanced situation where a patient needs even more skilful support. Further research is needed—in any case.

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