Drewes et al. [1] report on the evolution of new techniques for acquiring and analysing electroencephalography (EEG) data gathered during sleep. Their findings are important, but not new; they find high-frequency (alpha) intrusion into the deeper layers of non-dreaming sleep, with decreased slow-wave (delta) energy. The greater advance is technical [2]. By automating the data collection and analysis of the complex signals gathered every 2 s throughout the night, they make feasible much more rapid and thorough exploration of the origin and relevance of disturbed sleep in fibromyalgia (FM). Through tedious, time-consuming and highly innovative work on their part, they may free future researchers from the tedium, costs and frustrations of manual scoring. Let us review where we have been, and perhaps where we can go.

The field opened strongly with the studies of Moldofsky et al. [3, 4], published 20 yr ago. Most of the data were collected on paper, with a polygraph running at 15 mm/s rather than the usual 10 mm/s, to facilitate recognition of high-frequency waves. Over 10 h, this meant that 540 m of paper tracings were generated per one night study, nearly a third of a mile, all of which had to be carefully scored by hand. 'For four subjects one night of EEG was recorded on magnetic tape using a . . . FM tape recorder. Frequency spectrum analysis was later carried out on a . . . computer programmed to digitize the EEG data and perform a Fast Fourier Transform (FFT) . . . over a 2 second epoch.' The tracings that arose from this computer analysis have kept this observation alive over two decades of controversy about the reproducibility, specificity and meaning of these observations.

Two possible explanations for the sleep disturbance seemed obvious at the time. The patients were anxious; perhaps anxiety disturbed their sleep. They described severe pain; and perhaps pain disturbed their sleep. These two probably interacting factors seemed enough. As a psychiatrist, Moldofsky was interested in pain perception and made a huge leap further: perhaps sleep disturbance modulated pain perception. He therefore added to the experimental protocols studies of the effects of sleep disturbance in normal subjects. In the first study, the appearance of delta waves was the signal for an arousal stimulus, usually noise. This produced several effects: alpha intrusion, delta suppression, and an overnight increase in symptoms and measured tenderness. These observations were confirmed and extended in further studies, in which it was shown that disturbance of rapid eye movement (REM) sleep did not produce these effects.

In an earlier report, Drewes and colleagues [2] have succinctly discussed considerations underlying the technical differences between their techniques and others. They noted that alpha activity is 'often difficult to quantify visually, as only the most obvious . . . is seen'. Further, 'the EEG was preemphasized 20 dB/decade to expand amplitudes in high frequencies'. They changed the technique of data processing, because 'FFT is based on the assumption that the EEG is stationary, and, in fact, the EEG is generally regarded as a non-stationary stochastic signal', hence they have applied autoregressive techniques. Most obviously, they used the vastly superior computing power and storage capacity now available.

Further, they note [1] that there are a number of repetitive sleep cycles through the night. If non-REM (NREM) sleep is defined as stages 2–4 of non-dreaming sleep, NREM and REM sleep cycles were defined by the succession of a NREM period of at least 15 minutes and a REM period of at least 5 minutes duration. The importance of this is shown in their Fig. 4, which shows much higher ('restorative') delta power in the earlier cycles through the night, especially in control subjects.

These observations are a new beginning; there remains much to be done. First, there needs to be independent confirmation of Moldofsky's critical observations on the effects of experimental sleep deprivation. A preliminary report of such a study has appeared in abstract form [5].

Further questions suggest themselves; some technical, some clinical. Is there more than one alpha? This is very likely. The alpha waves in awake patients, lying relaxed, eyes closed, saying 'Omm', are likely different from those that appear in a patient entering stage 4 sleep, disturbed by having a buzzer sounding. We should remember that these patterns represent summary effects of many complex events, and only remotely reflect specific neurological events. Would a painful stimulus give a pattern different from that following a noise? Would pain from the neck give a different signal than pain from a calf muscle? Obviously, we need a kind of three-dimensional signal analysis pioneered in radiology in the development of computed tomography.

How do the sleep disturbances relate to the clinical picture in FM? Let us accept Moldofsky's suggestion that NREM sleep deprivation modulates neural responses. Past reports have emphasized the musculoskeletal symptoms and increased tenderness associated with sleep deprivation, but Moldofsky also reported fatigue, anorexia, nausea, diarrhoea, and mood changes,
associated with NREM deprivation, and loss of these features during the recovery period. During REM deprivation, a similar mixture of symptoms developed in some subjects, without measurable effects on tenderness [3, 4]. Symptom amplification affected not only painful stimuli, but other normally ignored irritants as well.

Fibromyalgia patients are sensitive to a wide variety of irritants in the external environment, such as cold, damp, noise, bright lights, cigarette smoke and other pollutants. They are similarly sensitive to internal stimuli, especially gastrointestinal and genitourinary symptoms. It is tempting to link these to the sleep disturbance, and other factors which have been found to affect tenderness, such as physical unfitness, gender, rheumatoid arthritis [6] and lupus, and chronic steroid therapy [7].

A common and disturbing set of symptoms described by these patients, but insufficiently studied in FM, impaired memory and concentration. It has been suggested for decades that normal sleep is important for memory processing and consolidation [8]. These speculations are strongly supported by two very different recent studies: one in rats learning spatial behavioural tasks [9] and one in humans learning to recognize old or new visual patterns [10]. In the first of these two studies, neuronal activity in the hippocampus related to memory processing occurred during slow-wave NREM sleep; in the second, disturbance of REM sleep had much greater effects on learning than did NREM deprivation. This warns us that both phases of sleep warrant attention, and may relate to different functional disturbances.

Impaired cognition, is of course, not specific for FM. An important and highly relevant report, published in this journal by Radanov et al. [11], described symptoms of sleep disturbance, impaired concentration and forgetfulness in patients following 'common whiplash' injuries. Tests of cognitive function were performed, and sleep disturbance, poor concentration, forgetfulness and score on test of information processing were all associated with poor outcome on multiple regression analyses.

It is even more important to recognize the interactions among FM, sleep disturbance and impaired cognition in patients with lupus. There is major danger that patients with this combination and inactive disease will be treated inappropriately for presumed central nervous system lupus. Steroids and cytotoxics are poor choices for patients with symptoms due to concomitant FM.

What are the therapeutic implications? Two strategies suggest themselves. The most common is to treat the sleep disturbance symptomatically, usually with tricyclic or related agents. These are seductive; simple to prescribe, with measurable early benefit. However, the study of Carette et al. [12] has shown that the minor benefit obtained by these agents is lost with time. At 6 months, treated patients were not measurably different than those receiving placebo, except that they were now adapted to a therapy that is not easy to withdraw without rebound insomnia. If the dose is then increased, the mental fogging produced by the drug further impairs cognitive function.

The other, neglected strategy is to deal with the origin of the sleep disturbance. The most obvious, treatable irritant is pain, and particularly pain arising in the neck and low back. During Moldofsky's experimental sleep-deprivation studies, the aching affected head, neck, shoulders and upper back (a distribution typical of referral from the neck [11, 13], and low back, 'hips' and legs, suggesting referral from the low back. The emergence of these symptom patterns during sleep deprivation, and disappearance during the recovery phase, suggests interaction between locally acting mechanical factors, which determine the pattern of symptoms, and the amplifying effect of non-restorative sleep, which determines symptom quantity. Mechanical and amplifying factors are both important, but in many patients the mechanical factors are more easily identified and treated; certainly, they must not be ignored. Evidence for the efficacy of this approach exists [13], but has not yet affected the behaviour of many health professionals. Perhaps this could be the topic of another editorial.

H. A. SMYTHE

Suite 647, Wellesley Hospital, 160 Wellesley Street East, Toronto, Ontario, M4Y 1J3, Canada

REFERENCES

CONCEPTUALIZING AND DEFINING OUTCOME

This year marks the twentieth anniversary of the first formal presentation of the draft [1] of what was to become the International Classification of Impairments, Disabilities, and Handicaps (ICIDH) [2]. The ICIDH describes itself as a manual of classification relating to the consequences of disease. As such it offers a conceptual basis for thinking about outcome associated with disease. In its schema, disease gives rise to impairment which is defined as 'any loss or abnormality of psychological, physiological, or anatomical structure or function'. Impairment itself may lead to disability, defined as 'any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being'. Impairments and disabilities, by interacting with the physical and social environment, can result in handicap. This is defined as a 'disadvantage for the given individual ... that limits or prevents the fulfilment of a role that is normal'. This progression from disease to handicap is illustrated in Fig. 1. To this has been added quality of life (QoL), which we believe to extend beyond the disease–handicap continuum, as it is mediated by a whole series of other factors. These include self-esteem, coping skills, age, gender and ethnicity [3–7].

The ICIDH has particular relevance to chronic disease generally and, specifically, rheumatic disease. We can imagine impairments such as pain, limited range of motion or fatigue, giving rise to disabilities, for example, in walking, dexterity or personal care. These impairments and disabilities may be further mediated by environmental factors to produce, for example, mobility handicap. Thereafter, personal attributes such as coping skills, or external factors such as level of disability benefits, will determine the impact of the disease and its consequences upon QoL. All the attributes of the continuum can be considered to be indications of outcome.

Conceptualizing outcome in this way helps us to think about what we are measuring. For example, consider the American College of Rheumatology’s (ACR) core disease activity measures of RA for use in clinical trials [8]. When we operationalize the conceptual continuum by specifying the various components of outcome, we find that much of the ACR core set clusters under disease (e.g. acute-phase reactant value) and impairment (e.g. pain). What is surprising is the increasing lack of specification as the proposed measures move away from the disease end of the continuum. For example, the disease activity measure ‘patient’s assessment of physical function’ can be operationalized by well-known measures such as the Stanford Health Assessment Questionnaire (HAQ) [9], the Arthritis Impact Measurement Scale (AIMS) [10] or the Quality of Well-Being Scale (QWBS) [11]. It is acknowledged that some of these instruments measure more than just physical function. However, given the salience of physical disabilities to arthritis (as shown in Fig. 1), can the instruments be considered equivalent? A brief perusal of these scales shows that they are quite different. For example, the QWBS enquires about ability to utilize public transport (handicap rather than disability) in its mobility domain, and mixes locomotor disability (walking) and mobility handicap (confined to bed or couch) in its physical activity domain. In contrast, the HAQ (in its UK version [12]) has eight sections dealing with upper and lower limb functions which by and large reflect the disabilities shown in Fig. 1. Did the ACR deliberately set out to provide such a broad specification under its ‘physical function’ domain? It is certainly inconsistent with the more narrowly defined measures of disease activity and impairment.

Recent developments in measurement techniques emphasize the need to have a clear conceptual basis. These developments centre upon ‘probabilistic conjoint measurement’ [13], which is more generally known under the label ‘the Rasch model’ [14]. This model formalizes desirable characteristics of measurement, e.g. unidimensionality. Fitting data to the model allows us to draw inferences that the observations we have made enjoy these desirable characteristics [15].

![Fig. 1.—Conceptualization of outcome in rheumatology.](image-url)