Pharmacology Biochemistry and Behavior, Vol. 56, No. 4, pp. 623–628, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(96)00429-7

A Theory of Postoperative Fatigue: An Interaction of Biological, Psychological, and Social Processes

PETER SALMON*[1] AND GEORGE M. HALL†

*Department of Clinical Psychology, Whelan Building, University of Liverpool, Liverpool L69 3BX, UK
†Department of Anaesthesia, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK

Received 16 August 1996; Revised 14 October 1996; Accepted 14 October 1996

SALMON, P. AND G. M. HALL. *A theory of postoperative fatigue: An interaction of biological, psychological, and social processes.* PHARMACOL BIOCHEM BEHAV **56**(4) 623–628, 1997.—The concept of postoperative fatigue has been developed to explain the feelings of malaise and the reduction in activity during the convalescent period that follows surgery in humans. Fatigue has been assumed to reflect the degree of surgical trauma and to be a consequence of muscle weakness caused by physiological sequelae of the trauma. The evidence is inconsistent with this reductionist view. Instead, we propose a theory that postoperative fatigue is based on an emotional and motivational change that has the function of ensuring inactivity so as to preserve homeostasis in vital systems in response to injury while preserving the physical capacity to respond to new challenge. This response, triggered by the patient's perception of the surgical stimulus, is prolonged by the influence of staff and patient expectations, which, in turn, reflect cultural beliefs in the necessity of convalescence. This theory can be tested by manipulation of clinical practice at pharmacological and psychological levels. © 1997 Elsevier Science Inc.

Surgery Fatigue Depression Anxiety Expectations

THE CONCEPT OF POSTOPERATIVE FATIGUE

MAJOR surgery is a trauma that provokes a constellation of hormonal, metabolic, hematological, and immunological responses that have been intensively investigated (26). There is a marked increase in secretion of catabolic hormones, such as catecholamines and cortisol, together with suppression of the key anabolic hormone, insulin. This results in mobilization of substrates, including glucose and amino acids, to maintain key synthetic processes in the postoperative period. Surgical trauma also rapidly increases circulating white blood cells and, reflecting tissue damage, cytokine secretion, particularly il-6. Changes in lymphocyte function are associated with immunosuppression, although the precise mechanisms that elicit these changes are still unknown. These responses are, of course, not specific to surgery but are also found with major trauma, massive hemorrhage, burns, etc. That is, surgery is only one of a variety of noxious stimuli that evoke this integrated physiological response (61,75). These changes have been regarded as deleterious: in particular, the marked loss of muscle protein that inevitably follows major surgery has been largely attributed to catabolic hormone secretion and regarded as a hindrance to the mobilization and recovery of the patient (26). Although the evidence to support the role of hormones in controlling muscle protein loss is weak (8,26), strenuous attempts are nevertheless made in modern anaesthetic and surgical practice to attenuate these responses. Although it has long been assumed that such procedures will enhance recovery (35,36), the evidence is inconclusive as to whether they can, alone, have a significant effect (3,41,59,80).

There are also striking behavioural and subjective responses to major surgery: it is common knowledge that patients feel weak or poorly and are often reluctant to mobilize or otherwise exert themselves. This state of postoperative malaise commonly extends for some weeks after major surgery (46). It is clinically important for two reasons. First, it is well known that immobilization impairs muscle function (2) and is also associated with serious complications such as deep-vein thrombosis and hence the risk of fatal pulmonary embolism. Second, regardless of physiological or functional changes, how

[1]To whom requests for reprints should be addressed. E-mail: psalmon@liv.ac.uk

a patient feels and functions will influence the patient's own evaluation of his or her recovery. Indeed, during the later convalescent period, once the patient has been discharged from hospital, this subjective criterion of recovery is likely to be crucial. It is therefore important that this subjective aspect of the response to surgical trauma receives as much scientific scrutiny as the biological components.

An important step in the investigation of this notion of postoperative malaise has been to call it fatigue. The scientific meaning of this term is derived from engineering (e.g., metal fatigue) and refers to the weakening of the structure and therefore function of a material by an excessive external demand. The concept of fatigue has influenced the way postoperative malaise is viewed. First, it has led to a stimulus–response model, in which postoperative fatigue is seen as a response that reflects directly the severity of the stimulus (18). Second, the assumption that postoperative fatigue is a manifestation of surgical trauma has led to the assumption that it should be explained solely on a physiological basis. The most popular explanation has been that muscle function is impaired as a consequence of the hormonal and metabolic response to surgery, compounded by immobilization and impaired nutrition (18).

The concept of postoperative fatigue has given rise to a large amount of research since it was first advanced (46). Our thesis is that the resulting body of data can no longer be accommodated by the concept that gave rise to it. Furthermore, we propose a theory of postoperative fatigue that integrates biological, psychological, and cultural factors and offers novel insights and therapeutic possibilities.

THE MEASUREMENT OF POSTOPERATIVE FATIGUE

Until recently, evidence about postoperative fatigue has arisen almost exclusively from the study of abdominal surgery. There is general agreement that fatigue increases after major abdominal surgery, although not after minor surgery, and persists for up to 30 days (10,14–17,19,56); occasionally fatigue has been noted to persist for up to 3 months (29). The majority of these reports were based on a single linear-analogue scale after it was introduced by Christensen et al. (14). Despite its widespread acceptance, the scale is ambiguous and, until recently, had not been critically evaluated. The scale refers both to subjective feeling (fatigue and tiredness) and to the capacity to perform daily activities, which may be more indicative of muscle weakness. There is empirical evidence that these two components are independent and that the linear-analogue scale is therefore bidimensional (10).

Nevertheless, a recent study using a validated adjective rating scale [Profile of Mood States (39)] has confirmed an increase in fatigue after surgery in a heterogeneous group of patients who were predominantly undergoing abdominal surgery (10). A second, similar report using the same adjective rating scale also showed an increase in fatigue postoperatively, but included many patients who were operated for malignancy (57). The introduction of improved methods of assessment of fatigue will enable more rigorous and discriminating analysis to be undertaken. In a contrasting, but no less severe, surgical model, and using a validated scale that separates mental from physical fatigue (12), we have recently shown that fatigue does not increase after hip and knee arthroplasty (1): postoperative fatigue merely reflects preoperative levels. Statistical findings mask the observation that some patients do not exhibit postoperative fatigue (17). Therefore, our understanding of postoperative fatigue has to accommodate the possibility that it is not a universal experience and is not a response to severe surgical stimuli in general but appears to be increased preferentially by abdominal surgery. This clearly contradicts the stimulus–response view that fatigue is related simply to the severity of surgical stimulus.

FATIGUE AS A PHYSICAL RESPONSE TO SURGICAL TRAUMA

The second assumption inherent in the concept of postoperative fatigue—that it reflects physical effects of surgical trauma—must also be questioned. The prolonged duration of fatigue is not compatible with physiological disturbances of muscle function, which are found only in the first 2 weeks (56). Moreover, hormonal and cytokine changes have returned to preoperative values within only a few days (26). Unsurprisingly, therefore, attempts to find a simple physiological explanation of fatigue have eluded extensive investigation. Kehlet's group investigated postoperative fatigue for over 10 years and were unable to provide a simple physiological explanation when the topic was reviewed in 1993 (18). Although they suggested that the important mechanisms included the endocrine–metabolic response, decreased nutritional intake, and immobilization, their extensive research has been unable to confirm the role of any one of these. In contrast, a separate surgical research group with wide experience in this area concluded recently that a simple mechanistic approach was inadequate and, indeed, that apparent muscular weakness is probably secondary to a central effect. They therefore argued for the involvement of other disciplines, including behavioural sciences, in exploring the basis of the central fatigue process (56).

FATIGUE AS AN ASPECT OF MOTIVATIONAL STATE

Like surgery, exhaustive exercise results in severe physiological disturbances in cardiovascular, hormonal, metabolic, and immunological systems (2). Moreover, fatigue is also a well-known consequence of exhaustive physical exercise. Despite being the subject of even greater investigation than fatigue after surgery, a simple physiological explanation for exercise-related fatigue has not been found. The attention to physiological disturbances to explain decline in physical performance may be mistaken. The offer of monetary reward was more effective in enhancing physical performance during endurance exercise than the correction of a major metabolic disturbance, namely low blood glucose concentration (22). In this case, therefore, the limiting factor for physical performance was motivational rather than physiological. Similarly, evidence that physical exercise reduces feelings of fatigue rather than increases them (67) is hard to reconcile with a simplistic view of fatigue as akin to physical exhaustion.

To view fatigue, tiredness, and exhaustion as motivational variables would be discrepant with the assumptions behind physiologically oriented research. However, it would be entirely consistent with the way these terms are used in everyday language. It has long been appreciated that words and expressions that convey emotional or motivational states are derived from physical metaphors (66). The emotional meaning of terms such as "tense," "scared stiff," or "depressed" is familiar, despite their ostensibly physical reference. Similarly, reports of being "exhausted," "worn out," or "lacking energy" usually signify that motivation is lacking rather than the physical capacity to perform the task (51). Indeed, it has been argued that complaint of fatigue is increasingly used in Western society as a socially sanctioned way of expressing motivational or emotional needs (64,73). To consider fatigue as a motivational variable permits a new way of explaining postoperative fatigue or malaise: not as a pathological response to surgical trauma, but as a component of a motivational change that ensues after surgery.

MOTIVATIONAL EFFECTS OF SURGERY

It is generally accepted that the physiological responses to surgery reflect mechanisms that have evolved to provide protection after serious injury (26). The primary requirement for an injured animal is to maintain homeostasis in essential physiological systems, such as circulating blood volume and glucose metabolism, at the expense of muscle protein and body fat. The characteristic lack of mobility and reduction in exertion after injury are probably essential in meeting these needs and also in enhancing healing of fractures and wounds. However, the injured animal is not isolated from external threats, such as predators, and its survival depends on its continued ability to respond to these threats. It is therefore implausible that the response to injury would have evolved such that homeostasis and healing were ensured by physiological changes that constrained activity. Consistent with this, it has long been known that complaints of pain and associated reduction in exertion following severe injury can be delayed by pressing external demands, such as those entailed on the battlefield (5,65): the injured soldier may continue to fight until the threats cease. Because the capacity to respond to trauma remains intact, control must be psychological: that is, the factors that determine whether to continue exertion or to withdraw and become inactive must be motivational rather than physiological.

Consider how this motivational process might be expressed in the surgical patient. Motivational states that inhibit behaviour in response to stress are well known clinically (25,40). Depression refers to the state in which an individual does not wish to move; anxiety describes the state in which he is too frightened to do so. It is possible that depression and anxiety become labelled, in the physiologically oriented context of the surgical ward, as fatigue. This suggestion is consistent with the way that a single internal state can be labelled by the person experiencing it in emotional or physical terms, depending on the context (43). This analysis therefore suggests that postoperative fatigue should be viewed as an aspect of emotional state after surgery. From this argument, we predict that measurements of fatigue in surgical patients should relate closely to depression and anxiety.

In contrast with the intensive and extensive search for physiological correlates of fatigue, there has been very little exploration of its psychological correlates. The time course of emotional changes postoperatively suggests that these factors must be considered seriously. Anxiety can be elevated for many weeks after surgery (32). Depression has been less commonly measured but, where it has, it responded similarly to anxiety (13,70). Nevertheless, in an influential study, Christensen et al. (15) inferred that fatigue was physiologically rather than psychologically based, because the increase in fatigue after abdominal surgery was uncorrelated with preoperative anxiety. This conclusion has been reasserted subsequently (19) and has become an influential one (18). It is, however, a surprising conclusion because Christensen et al. (15) did show that, preoperatively, fatigue correlated highly ($r = 0.68$) with state-anxiety and that the increase in fatigue to 30 days postoperatively correlated with the increase in anxiety over the same period ($r = 0.65$). We have also shown that both mental and physical fatigue 30 days after coronary artery bypass graft surgery correlated with anxiety and depression measured at the same time (44). More recently, we have confirmed that fatigue before and 7 weeks after major joint arthroplasty correlated with negative mood measured at the same times (1). We showed, furthermore, that patients who reported mental fatigue postoperatively tended to be those who had reported more negative mood preoperatively; this suggested that a feeling that is experienced, preoperatively, as low mood and lack of motivation is relabelled following surgery as fatigue (1). Overall, these findings provide convincing support for the hypothesis that postoperative fatigue is an aspect of emotional distress. This conclusion should not be surprising in view of the close association of fatigue with depression in patients with cancer (28) or chronic fatigue syndrome (31,74) and with depression and anxiety in pregnant women (45).

That motivational states become expressed as fatigue is not merely of semantic interest. The expression of emotional distress in physical terms (somatization) has long been known to confuse medical management (21,23,54). Inappropriate investigation and treatment ensue inevitably and so prolong and intensify the dependency of the patient on medical services. For instance, in a recent study of chronic fatigue patients, those who believed firmly in a physical basis to their fatigue had the worst prognosis (76). In this way, convalescence after surgery could be prolonged—a point to which we return below.

SURGERY AS A PSYCHOLOGICAL STIMULUS

The corollary of regarding fatigue as a psychological response is that the stimulus that triggers it must have a psychological component. Although the sequelae of surgery are usually attributed to the physical insult, surgery inevitably entails important psychological threats (48,71), and the probability of a psychological influence on the hormonal and metabolic response to surgery has been acknowledged for many years (75). We and others have now shown that the endocrine stress response to surgery can be influenced by psychological interventions (37,38,53,77), and a large literature attests to the ability of psychological interventions to influence various indicators of clinical outcome (50). These findings show that many of the consequences of surgery reflect not only the severity of the trauma but also the patient's perception of the event. We suggest that fatigue should therefore also be considered as a response to patients' perception of the surgical stimulus. This could explain the findings, described above, that fatigue occurs after abdominal surgery but not major joint arthroplasty (1). Whereas abdominal surgery generally signifies a threat to well-being or mortality, arthroplasty usually presages a marked improvement in function and well-being. If fatigue is sensitive to psychological aspects of the surgical stimulus, it follows that it must reflect also the expectations patients bring to surgery and that then influence their perception of it. These expectations reflect, in turn, cultural and historical influences.

It is a cultural expectation, held both by patients and by staff responsible for their care, that fatigue is an inevitable consequence of major surgery and that it will prevent a rapid return to normal activities. Unsurprisingly, there is long-standing evidence that people behave in ways that reflect their expectations (47) and that this process can, as the placebo effect, influence effects of medical and surgical treatment (30,62). It is therefore not surprising that expectations of outcome influence how patients feel after surgery (24). It is known that withdrawal from normal activity increases depression (4)

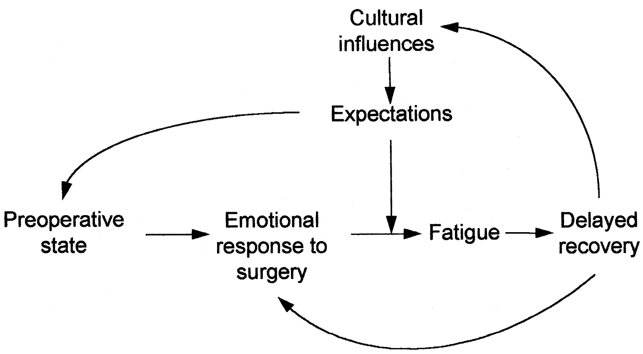

FIG. 1. A model of psychological processes involved in the origin and maintenance of postoperative fatigue. The emotional response to surgery, which is influenced by aspects of a patient's preoperative state, becomes labelled as fatigue in response to patient and staff expectations. Because of this, recovery is delayed, which tends to impair emotional state further and contributes to the expectation of prolonged convalescence.

and that, conversely, physical activity relieves depression (11,49,78). Postoperative fatigue could in this way become a crucial part of a vicious circle whereby convalescence is prolonged.

One way to define the role of cultural influences is to compare recovery between humans and animals, which are presumably less affected by such factors. Although subjective fatigue cannot be compared between humans and other species, comparisons can be made at the level of overt behaviour. On this basis, recovery after surgical or other injury in animals is very rapid, with apparently no convalescence required. For example, it has been noted that fatigue is a peculiarly human phenomenon and that animals return to normal activity much more quickly: for example, greyhounds who underwent hysterectomy were able to return to *racing* 3 weeks after surgery, a strikingly short period (56). No comparable data exist for return to strenuous physical activity in humans although, anecdotally, children and highly motivated adults, such as athletes, have shorter convalescence. The duration of hospitalization for a given procedure varies between countries, between hospitals, and across time: a survey in the UK confirmed a gradual reduction from 1948 until 1983 (20). Such variability does not simply reflect variation in surgical techniques or in pressure of waiting lists (20). Instead, it is inescapable that variability in hospital stay and convalescence reflects variable and changing expectations. The slow rate of decline in hospital stay (20) attests to the strength of these expectations. We therefore speculate that postoperative fatigue and convalescence represent the cultural prolongation of the biological and psychological processes of self-restraint that have evolved to protect us after injury.

CLINICAL IMPLICATIONS

This novel analysis of fatigue is summarized in Fig. 1 and suggests various points at which novel interventions to facilitate recovery can be undertaken. The immediate emotional response to surgery is the obvious starting point and might be susceptible to psychological modification. The main thrust of research into psychological interventions in surgery has, however, been on the preoperative period, despite evidence that preoperative emotional state is poorly related to aspects of recovery other than postoperative emotional state. Rather than focusing directly on emotional state, the design of psychological interventions has been theoretically guided, primarily by psychological ideas concerned with the benefits of coping, information, and social support in preparing for, and responding to, stress [see (34,50) for a meta-analysis and review, respectively]. Extensive effects on clinical outcome have been described. Some of these, such as reductions in analgesic consumption and duration of hospital stay, are ambiguous indicators of a patient's state. Nevertheless, sufficient evidence attests to the ability of a variety of techniques to improve the patient's mood postoperatively as well as some significant physiological indices of recovery. Attempts to relieve anxiety directly have been limited and have focused, for theoretical reasons, on the preoperative period; nevertheless, relaxation training has been successful in reducing postoperative anxiety (38). Although there are proven techniques of behavioural and cognitive therapy for relieving anxiety and depression that are used routinely in clinical settings, these have not yet been evaluated in surgery. Our theory would predict that they would be beneficial, although they should be targeted on the postoperative convalescent period, rather than preoperatively. It is interesting that a recent report attests to the ability of cognitive therapy to reduce fatigue in chronic fatigue syndrome (63).

Realistically, however, the hospital environment does not lend itself to intensive and protracted psychological interventions. A pharmacological approach is a more practical alternative. At present, benzodiazepines are generally used for anxiolytic purposes but, as with psychological approaches, are applied during the preoperative period as premedication. Postoperatively, emotional state is usually disregarded and pain relief, commonly with morphine, takes precedence in spite of evidence that the level of emotional distress after medical and surgical procedures is largely independent of pain (33,52,55). Central effects of morphine administered clinically are commonly sedative (69); morphine could therefore even impair the rate of recovery. There is, in contrast, evidence that high-dose glucocorticoid 90 min before major abdominal surgery improved fatigue postoperatively (58,60). This surprising finding could be explained by the well-known mood-enhancing properties of steroids and therefore supports our hypothesis. However, steroids have an immunosuppressive action, and the effects of more specific anxiolytic and antidepressant drugs should be investigated. This approach will need adequate treatment preoperatively, but also continuation through the convalescent period. Because of the putative involvement of 5-HT systems in anxiety and depression (40) as well as fatigue (9,27,42), drugs that act specifically on these systems may repay particular investigation.

Nutritional interventions have hitherto been regarded as ways of providing suitable fuels for muscle function after surgery (18). However, our analysis suggests that a very different mode of action should be considered. Although the evidence is confusing and often conflicting, there have been claims, with some empirical support, that a variety of major nutrients and micronutrients improve mood (6,7,72,79) and enhance physical performance with reduction in fatigue (9,27,42,68). Future resolution of the currently inconsistent picture may indicate nutritional interventions that could improve postoperative recovery by reducing fatigue and associated emotional impairment.

The expectations of the patient and of the responsible staff are crucial elements of our theory, but have received very little attention in the literature. Psychological interventions to change patients' expectations have not been tested systematically, although approaches based on educational techniques or visual imagery (37) might be employed in this way. A recent report described a dramatic improvement in the rate of recovery from major colonic surgery in elderly patients: some were able to return home 2 days after operation (3). The management of these patients was a novel combination of factors thought to enhance recovery. Surgery was conducted with laparoscopic assistance to minimize tissue damage, pain relief was provided by regional anaesthesia, opiates were avoided where possible, and early nutrition was instituted. These technical aspects of care were supplemented by a vigorous program of exercise and rehabilitation that started immediately after surgery. It is possible that the critical factor in this package was one not identified by the authors. It is unlikely that such a novel program could have been instituted without a marked change in expectations of both staff and patients. According to our theory, change in expectations should receive as much attention as the biological interventions in attempting to explain effects of this treatment regime.

Routinely, it will be more influential to manipulate expectations at the level of a surgical team, ward, hospital, or even population than at the level of the individual patient. In practice, however, it is likely to be staff rather than patient expectations that are more resistant to change, because the reductions in hospital stay and medical demands of convalescence will conflict with professional interests. In practice, change in expectations of both staff and patients will influence and also reflect changes at the cultural level. Inevitably, therefore, there will be a time lag between acceptance of the validity of the ideas advanced here and changes in routine clinical practice.

CONCLUSION

The need for theories of medical practice that encompass social, psychological, and biological processes is widely asserted. To date, however, few theories of this kind exist. We have linked established ideas in behavioural, biological, and clinical sciences so as to produce a theory that is testable by changes in clinical practice at different levels. The theory therefore provides a model for the development of attempts to understand other problems in medical care that defy solution by conventional biomedical interventions.

ACKNOWLEDGEMENTS

This work was supported by the UK Medical Research Council. We are grateful to Sarah Peters for comments on a draft of this manuscript.

REFERENCES

1. Aarons, H.; Forester, A.; Hall, G.; Salmon, P.: Fatigue after major joint arthroplasty: Relationship to preoperative fatigue and postoperative emotional state. J. Psychosom. Res. 1996; 41:225–233; 1996.
2. Astrand, P. O.; Rodahl, K., eds.: Textbook of work physiology: Physiological basis of exercise. Singapore: McGraw-Hill; 1986.
3. Bardram, L.; Funchjensen, P.; Jensen, P.; Crawford, M. E.; Kehlet, H.: Recovery after laparoscopic colonic surgery with epidural analgesia and early oral nutrition and mobilization. Lancet 345:763–764; 1995.
4. Beck, A. T.; Rush, A. J.; Shaw, B. F.; Emery, G.: Cognitive therapy of depression. New York: Guilford; 1979.
5. Beecher, H. K.: Relationship of significance of wound to the pain experienced. JAMA 161:1609–1613; 1956.
6. Benkelfat, C.; Ellenbogen, M. A.; Dean, P.; Palmour, R. M.; Young, S. N.: Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. Arch. Gen. Psychiatry 51:687–697; 1994.
7. Benton, D.; Haller, J.; Fordy, J.: Vitamin supplementation for 1 year improves mood. Neuropsychobiology 32:98–105; 1995.
8. Bessey, P. Q.; Walters, J. M.; Bier, D. M.; Wilmore, D. W.: Combined hormonal infusion stimulates the metabolic response to injury. Ann. Surg. 200:264–281; 1984.
9. Blomstrand, E.; Hassmen, P.; Ekblom, B.; Newsholme, E. A.: Administration of branched-chain amino acids during sustained exercise: Effects on performance and on plasma concentration of some amino acids. Eur. J. Appl. Physiol. 63:83–88; 1991.
10. Buxton, L. S.; Frizelle, F. A.; Parry, B. R.; Pettigrew, R. A.; Hopkins, W. G.: Validation of subjective measures of fatigue after elective operations. Eur. J. Surg. 158:393–396; 1992.
11. Byrne, A. E.; Byrne, D. G.: The effect of exercise on depression, anxiety and other mood states: A review. J. Psychosom. Res. 37:565–574; 1993.
12. Chalder, T.; Berelowitz, G.; Pawlikowska, T.; Watts, L.; Wessely, S.; Wright, D.; Wallace, E. P.: Development of a fatigue scale. J. Psychosom. Res. 37:147–153; 1993.
13. Chapman, C. R.; Cox, G. B.: Determinants of anxiety in elective surgery patients. In: Spielberger, C. D.; Sarason, I. G., eds. Stress and anxiety, vol. 4. Washington, DC: Hemisphere; 1977:269–290.
14. Christensen, T.; Bendix, T.; Kehlet, H.: Fatigue and cardiorespiratory function following abdominal surgery. Br. J. Surg. 69:417–419; 1982.
15. Christensen, T.; Hjortso, N. C.; Mortensen, E.; Riis-Hansen, M.; Kehlet, H.: Fatigue and anxiety in surgical patients. Acta Psychiatr. Scand. 73:76–79; 1986.
16. Christensen, T.; Hougard, F.; Kehlet, H.: Influence of pre- and intraoperative factors on the occurrence of postoperative fatigue. Br. J. Surg. 72:63–65; 1985.
17. Christensen, T.; Kehlet, H.: Postoperative fatigue and changes in nutritional status. Br. J. Surg. 71:473–476; 1984.
18. Christensen, T.; Kehlet, H.: Postoperative fatigue. World J. Surg. 17:220–225; 1993.
19. Christensen, T.; Stage, J. G.; Galbo, H.; Christensen, N. J.; Kehlet, H.: Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. Surgery 105:46–50; 1989.
20. Coulter, A.; McPherson, K.: Waiting times and duration of hospital stay for common surgical operations: Trends over time. Community Med. 9:247–253; 1987.
21. Craig, T. K. J.; Boardman, A. P.: Somatization in primary care settings. In: Bass, C. M., ed. Somatization: Physical symptoms and psychological illness. Oxford, UK: Blackwell; 1990:73–103.
22. Felig, P.; Cherif, A.; Minagawa, A.; Wahren, J.: Hypoglycemia during prolonged exercise in normal men. N. Engl. J. Med. 306:895–900; 1982.
23. Fink, P.: Surgery and medical treatment in persistent somatizing patients. J. Psychosom. Res. 36:439–447; 1992.
24. Flood, A. B.; Lorence, D. P.; Ding, J.; McPherson, K.; Black, N. A.: The role of expectations in patients' reports of post-operative outcomes and improvement following therapy. Med. Care 31: 1043–1056; 1993.
25. Glue, P.; Nutt, D. J.; Coupland, N.: Stress and psychiatric disorder. In: Stanford, S. C.; Salmon, P., eds.: Stress from synapse to syndrome. London: Academic Press; 1993:53–73.
26. Hall, G. M.: Endocrine and metabolic responses to surgery and anaesthesia. In: Nimo, W. S.; Rowbotham, D. J.; Smith, G., eds. Anaesthesia, 2nd ed. Oxford, UK: Blackwell; 1994:595–605.
27. Hassmen, P.; Blomstrand, E.; Ekblom, B.; Newsholme, E. A.: Branched-chain amino acid supplementation during a 30-km competitive run: Effects on mood and cognitive performance. Nutrition 10:405–410; 1994.

28. Hickok, J. T.; Morros, G. R.; McDonald, S.; Bellg, A. J.: Frequency and correlates of fatigue in lung-cancer patients receiving radiation-therapy—Implications for management. J. Pain Symptom Manage. 11:370–377; 1996.
29. Hill, G. L.; Douglas, R. G.; Schroeder, D.: Metabolic basis for the management of patients undergoing major surgery. World J. Surg. 17:146–153; 1993.
30. Ho, K. H.; Hashish, I.; Salmon, P.; Freeman, R.; Harvey, W.: Reduction of post-operative swelling by a placebo effect. J. Psychsom. Res. 32:197–205; 1988.
31. Hotopf, M. H.; Wessely, S.: Viruses, neuroses and fatigue. J. Psychosom. Res. 38:499–514; 1994.
32. Johnston, M.: Anxiety in surgical patients. Psychol. Med. 10:145–152; 1980.
33. Johnston, M.: Dimensions of recovery from surgery. Int. Rev. Appl. Psychol. 33:505–520; 1984.
34. Johnston, M.; Vogele, C.: Benefits of psychological preparation for surgery: A meta-analysis. Ann. Behav. Med. 15:245–256; 1993.
35. Kehlet, H.: Anesthetic technique and surgical convalescence. Acta Chir. Scand. Suppl. 550:182–191; 1988.
36. Kehlet, H.; Moesgaard, F.: Prophylaxis against postoperative complications in gastroenterology. Scand. J. Gastroenterol. 31:218–224; 1996.
37. Manyande, A.; Berg, S.; Gettins, D.; Stanford, S. C.; Marks, D.; Salmon, P.: Preoperative rehearsal of active coping imagery influences subjective and hormonal responses to surgery. Psychosom. Med. 57:177–182; 1995.
38. Manyande, A.; Chayen, S.; Priyakumar, P.; Smith, C. C. T.; Hayes, M.; Higgins, D.; Kee, S.; Phillips, S.; Salmon, P.: Preoperative relaxation increases endocrine responses to surgery. Psychosom. Med. 54:275–287; 1992.
39. McNair, D. M.; Lorr, M.; Droppleman, L. F.: EITS manual for the profile of mood states. San Diego, CA: Educational and Industrial Testing Service; 1971.
40. McNaughton, N.: Stress and behavioural inhibition. In: Stanford, S. C.; Salmon, P., eds. Stress from synapse to syndrome. London: Academic Press; 1993:191–206.
41. Moiniche, S.; Bulow, S.; Hesselfedt, P.; Hestbaek, A.; Kehlet, H.: Convalescence and hospital stay after colonic surgery with balanced analgesia, early oral-feeding, and enforced mobilization. Eur. J. Surg. 161:283–288; 1995.
42. Newsholme, E. A.; Blomstrand, E.: Tryptophan, 5-hydroxytryptamine and a possible explanation for central fatigue. Adv. Exp. Med. Biol. 384:315–320; 1995.
43. Pennebaker, J. W.: The psychology of physical symptoms. New York: Springer-Verlag; 1982.
44. Pick, B.; Molloy, A.; Hinds, C.; Pearce, S.; Salmon, P.: Postoperative fatigue following coronary artery bypass surgery: Relationship to emotional state and to the catecholamine response to surgery. J. Psychosom. Res. 38:599–607; 1994.
45. Reaves, N.; Potemp, A. K.; Gallo, A.: Fatigue in early pregnancy: An exploratory study. J. Nurse-Midwifery 36:303–309; 1991.
46. Rose, E. A.; King, T. C.: Understanding post-operative fatigue. Surg. Gynecol. Obstet. 147:97–101; 1978.
47. Rosenthal, R.: Experimenter effects in behavioral research. New York: Appleton-Century-Crofts; 1966.
48. Salmon, P.: Psychological factors in surgical stress: Implications for management. Clin. Psychol. Rev. 12:681–704; 1992.
49. Salmon, P.: Emotional effects of physical exercise. In: Stanford, S. C.; Salmon, P., eds. Stress: From synapse to syndrome. London: Academic Press; 1993:395–419.
50. Salmon, P.: Psychological factors in surgical recovery. In: Gibson, H. B., ed. Psychology, pain and anaesthesia. London: Chapman and Hall; 1994:229–258.
51. Salmon, P.: Nutrition, cognitive performance and mental fatigue. Nutrition 10:427–428; 1994.
52. Salmon, P.; Drew, N. C.; Miller, R.: Women's anticipation and experience of childbirth: The independence of fulfilment, unpleasantness and pain. Br. J. Med. Psychol. 63:255–259; 1990.
53. Salmon, P.; Evans, R.; Humphrey, D.: Anxiety and endocrine changes in surgical patients. Br. J. Clin. Psychol. 25:135–141; 1986.
54. Salmon, P.; May, C. R.: Patients' influence on doctors' behaviour: A case study of patient strategies in somatization. Int. J. Psychiatry Med. 25:319–329; 1995.
55. Salmon, P.; Shah, R.; Berg, C.; Williams, C.: Evaluating customer satisfaction with colonoscopy. Endoscopy 26:342–346; 1994.
56. Schroeder, D.; Hill, G. L.: Postoperative fatigue: A prospective physiological study of patients undergoing major abdominal surgery. Aust. N.Z. J. Surg. 61:774–779; 1991.
57. Schroeder, D.; Hill, G. L.: Predicting postoperative fatigue: Importance of preoperative factors. World J. Surg. 17:226–231; 1993.
58. Schulze, S.; Moller, I. W.; Bang, U.; Rye, B.; Kehlet, H.: Effect of combined prednisolone, epidural analgesia and indomethacin on pain, systemic response and convalescence after cholecystectomy. Acta Chir. Scand. 156:203–209; 1990.
59. Schulze, S.; Roikjaer, O.; Hasselstrom, L.; Jensen, N. H.; Kehlet, H.: Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not the systemic response and convalescence after cholecystectomy. Surgery 103:321–327; 1988.
60. Schulze, S.; Sommer, P.; Bigler, D.; Honnens, M.; Shenkin, A.; Cruickshank, A. M.; Bukhave, K.; Kehlet, H.: Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response after colonic surgery. Arch. Surgery 127:325–331; 1992.
61. Selye, H.: The stress of life. New York: McGraw-Hill; 1976.
62. Shapiro, A. K.; Morris, L. A.: The placebo effect in medical and psychological therapies. In: Garfield, S. L.; Bergin, A. E., eds. Handbook of psychotherapy and behavior change. New York: Wiley; 1978.
63. Sharpe, M.; Hawton, K.; Simkin, S.; Surawy, C.; Hackmann, A.; Klimes, I.; Peto, T.; Seagroatt, V.: Cognitive therapy of the chronic fatigue syndrome: A randomised controlled trial. Br. Med. J. 312:22–26; 1996.
64. Shorter, E.: From paralysis to fatigue: A history of psychosomatic illness in the modern era. New York: Free Press; 1992.
65. Skevington, S.: Psychology of pain. Chichester, UK: Wiley; 1995.
66. Skinner, B. F.: About behaviorism. London: Cape; 1974.
67. Thayer, R. E.: Energy, tiredness and tension effects of a sugar snack versus moderate exercise. J. Pers. Soc. Psychol. 52:119–125; 1987.
68. van Hall, G.; Raaymakers, J. S.; Saris, W. H.; Wagenmakers, A. J.: Ingestion of branched-chain amino acids and tryptophan during sustained exercise in man: Failure to affect performance. J. Physiol. Lond. 486:789–794; 1995.
69. Vickers, M. D.; Morgan, M.; Spencer, P. S. J.: Drugs in anaesthetic practice, 7th ed. Oxford, UK: Butterworth-Heinemann; 1991.
70. Vogele, C.; Steptoe, A.: Physiological and subjective stress responses in surgical patients. J. Psychosom. Res. 30:205–215; 1986.
71. Volicer, B. J.; Bohannon, M. W.: A hospital stress rating scale. Nurs. Res. 24:352–359; 1975.
72. Wardle, J.: Cholesterol and psychological well-being. J. Psychosom. Res. 39; 549–562; 1995.
73. Ware, N. C.; Kleinman, A.: Culture and somatic experience: The social course of illness in neurasthenia and chronic fatigue syndrome. Psychosom. Med. 54:546–560; 1992.
74. Wessely, S.; Powell, R.: Fatigue syndromes: A comparison of chronic 'postviral' fatigue with neuromuscular and affective disorders. J. Neurol. Neurosurg. Psychiatry 52:940–948; 1989.
75. Wilmore, D. W.; Long, J. M.; Mason, A. D.; Pruitt, B. A.: Stress in surgical patients: A neurophysiologic reflex response. Surg. Gynecol. Obstet. 142:257–269; 1976.
76. Wilson, A.; Hickie, I.; Lloyd, A.; Hadzi-Pavlovic, D.; Boughton, C.; Dwyer, J.; Wakefield, D.: Longitudinal study of outcome of chronic fatigue syndrome. Br. Med. J. 308:756–759; 1994.
77. Wilson, H. F.: Behavioral preparation for surgery: Benefit or harm? J. Behav. Med. 4:79–102; 1981.
78. Yeung, R. R.: The acute effects of exercise on mood state. J. Psychosom. Res. 40:123–141; 1996.
79. Young, S. N.: The use of diet and dietary components in the study of factors controlling affect in humans: A review. J. Psychiatry Neurosci. 18:235–244; 1993.
80. Zeiderman, M. R.; Welchew, E. A.; Clark, R. G.: Influence of epidural analgesia upon postoperative fatigue. Br. J. Surg. 78: 1457–1460; 1991.