could be the use of prophylactic *Pneumocystis*-active agents in patients receiving long-term, high-dose inhaled or oral corticosteroid therapy. Unraveling these complex issues ought to be possible in larger longitudinal cohort-based studies.

A possible weakness of the current study is that it employed crude extracts from murine *P. murina* infections, which may not be entirely consistent with human *P. jirovecii* antigen sensitization and are not suitable for skin hypersensitivity testing. To further develop the tools and approaches needed to further define the role on *Pneumocystis* in asthma, systematic definition of human *Pneumocystis* antigens could be very useful, opening a door to direct sensitization studies, assessment of individual cellar responses, and therapeutic vaccination. ∎

Anand Shah, M.R.C.P., M.B. B.S.
Darius Armstrong-James, M.R.C.P., Ph.D.
National Heart and Lung Institute
Imperial College London
London, United Kingdom

ORCID ID: 0000-0002-1014-7343 (D.A.-J.).

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Muscle Regeneration after Critical Illness: Are Satellite Cells the Answer?

In 1985, Op de Coul and colleagues reported 12 patients who had developed profound skeletal muscle weakness without sensory

impairment after mechanical ventilation for 6 days or longer (1). They attributed the weakness to the use of neuromuscular blockade, but in fact their patients were also exposed to other factors now believed to contribute to intensive care unit–acquired weakness (ICUAW), including corticosteroids, aminoglycosides, and, most importantly, multiorgan failure. These patients followed a variable course: three died during follow up, and only seven made a full recovery over 2 to 6 months.

In the intervening 30 years, an explosion has occurred in the number of patients receiving intensive care, their illness severity, and the effectiveness of organ support. As a consequence, an increasing number of survivors, recently estimated to be approximately 75,000 patients annually in the United States (2), develop ICUAW. Critical illness is followed, even up to 5 years later, by functional disability, including impaired exercise capacity (3). The etiology is probably multifactorial, but it is at least in part ascribable to ICUAW and may persist despite exercise training; therefore, effective therapeutic approaches have great potential to improve quality of life in survivors and to be economically attractive. However, identifying these approaches has been hampered by the fact that patients with ICUAW are typically heterogeneous in terms of their comorbidities, their reason for ICU admission, and (in this context) the potentially damaging therapies (e.g., neuromuscular blocking agents) to which they might have been exposed. Similarly, at a physiological level controversy remains regarding the extent to which ICUAW should be considered a muscle disorder or of neurogenic origin.

The molecular mechanisms underlying ICUAW have been recently studied; the strength of this approach is that it moves focus toward maximizing function in the face of multiple etiological factors. As a result of the work of Puthucheary and coworkers, we have greater insight into the early changes taking place in the skeletal muscle of patients admitted to the ICU (4). Briefly, myonecrosis was observed in approximately half the patients, and rates of muscle protein breakdown were increased throughout the first week of ICU admission; interestingly, rates of muscle synthesis were reduced at the point of ICU admission but were similar to fasted healthy control subjects by Day 7. Until now, however, we had very little insight into mechanisms determining skeletal muscle mass over longer periods. In this issue of the *Journal*, dos Santos and colleagues (pp. 821–830) studied a prospectively recruited cohort of patients who required mechanical ventilation for 1 week or longer after discharge from their index admission, which had lasted between 9 and 88 days (5). From an initial pool of 82 eligible and 27 consented patients, 11 were studied at both 7 days and 6 months. Strengths of these unique data include the prospective way in which they were gathered and the comprehensive clinical and histological data obtained. As expected, quadriceps strength improved, to a variable extent, between Day 7 and 6 months and was universally reduced at Day 7 compared with published normal values. Recovery of quadriceps muscle bulk, assessed as computed tomography–defined midthigh cross-sectional area, was similarly variable, and in three patients the authors report that at 6 months there was a marked diminution of the ratio between voluntary contraction force and cross-sectional area (termed muscle-specific force), suggesting the interesting hypothesis that the regenerated muscle is of "poor quality." At 7 days, there was evidence of increased ubiquitination (suggesting an increased rate of muscle breakdown), but this had reduced at 6 months to levels that were not different from library samples obtained from healthy volunteers. Why then should quadriceps weakness and atrophy be present at 6 months, if there is neither increased breakdown nor reduced synthesis?

Here the authors provide new data by determining the number of satellite cells. Satellite cells are muscle progenitor cells that differentiate into myoblasts and fuse to myofibers, as part of the process of muscle regeneration. Thus, for example, patients with chronic obstructive pulmonary disease (COPD) receiving exercise training exhibited increased satellite cell numbers within 24 hours, which persisted for 2 months of training (6). Satellite cells are sparse, and it has been estimated that a minimum of 50 type I and 75 type II fibers should be assessed to draw meaningful conclusions even in young adults (7). dos Santos and colleagues were obliged to accept those specimens with 50 or more visible fibers only, presumably because biopsies from patients in the ICU are necessarily difficult to obtain (5). With this reservation, their finding that patients with demonstrable muscle atrophy at 6 months had fewer satellite cells than those without atrophy at this time point is relevant, because it implies that a reduced ability to regenerate impairs restoration of muscle mass after critical illness and explains variation between individuals.

A loss of muscle bulk may be considered to be a function both of the magnitude of the insult and the susceptibility to that insult. MicroRNAs (miRs) are noncoding RNAs that exert biologically important effects. miR-1 promotes myotube formation, and thus one candidate mechanism determining the magnitude of the insult may be reduced miR-1 expression, which we found to be substantially suppressed in a study of 20 patients with a median length of stay of 20 days (8) and also in patients with COPD (9). Reduced regeneration was observed by Thériault and colleagues (10) and by ourselves (11) in patients with COPD with a low fat-free mass index. In our studies, reduced regeneration was associated with differential expression of genes from imprinted genetic loci, suggesting a role for epigenetics and DNA methylation in determining the rate of regeneration in response to the stress of disease (11).

Understanding the mechanisms by which patients recover muscle in response to the loss associated with critical illness is important in developing appropriate therapeutic approaches to relieve the burden of ICUAW on patients. By identifying satellite cell number as a potential factor contributing to the longer-term response of individuals to ICUAW, the study by dos Santos and colleagues raises the possibility that the capacity of individuals to regenerate may determine recovery of skeletal muscle function after critical illness (5); the contribution of epigenetic factors to this recovery may be an interesting avenue of exploration. ∎

Michael I. Polkey, Ph.D.
Mark J. Griffiths, M.D.
National Institute for Health Research Respiratory Biomedical Research Unit
Royal Brompton and Harefield National Health Service Foundation Trust and
  Imperial College
London, United Kingdom

Paul R. Kemp, Ph.D.
National Institute for Health Research Respiratory Biomedical Research Unit
Royal Brompton and Harefield National Health Service Foundation Trust and
  Imperial College
London, United Kingdom
and
National Heart and Lung Institute
Imperial College
London, United Kingdom

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Advancing a Third Revolution in Critical Care

By the 1970s, a revolution was underway in critical care. The field distinguished itself professionally, claiming that critical care medicine was a distinctive body of expertise. The closed intensive care unit (ICU) was born (1). This revolution argued that a well-organized approach, not merely individual excellence, could save the lives of the very sick.

By the 1990s, a second revolution began in critical care. Through a tumultuous series of debates, we recognized that prolonging life ought not to be the sole goal of critical care. ICU practitioners assumed ownership of acute care of the dying (2). Excellence in family meetings, shared decision making, and symptom palliation were recognized as core ICU competencies, alongside resuscitation and ventilator management. This second revolution argued that a well-organized approach can provide a good death (or a good dying process) to those we cannot save.

This decade, a third revolution is underway in critical care. It is born of dissatisfaction with the simple dichotomization of alive versus dead. It builds on our growing expertise in both resuscitation and end-of-life care, but extends the ambition of the ICU to helping patients thrive after surviving their critical illness. This third revolution argues that a well-organized approach can help those who survive critical illness live full new lives; lives not the same as they were before, necessarily, but also not necessarily less.

Each revolution is unfinished, but no less important for that. Each combines ambition, partnership, practice innovation, and science. Helping each revolution are useful conceptual simplifications that cognitively organized previously disparate problems and practices. In the first revolution: "shock" (3), "resuscitation," and "acute respiratory distress syndrome" (4); in the second: a "good death" and "acute care of the dying" (5).

The third revolution in critical care is still searching for that grand simplification to help us improve survivorship. One area of particular interest is those patients who linger in the ICU, neither thriving nor dying (6). Although they comprise a minority of those we serve, they may account for a disproportionate number of bed-days and, given their emotional salience to many clinicians, even more of our recalled experience of providing ICU care.

Herridge and colleagues and the Canadian Critical Care Trials Group began the RECOVER program in 2007 to study these patients. In this issue of the *Journal* (pp. 831–844), they report that they recruited ICU patients for 7 years, from 2007 through 2014, at ICUs across Canada (7). They found 1,013 patients aged 16 years and older who had been mechanically ventilated for at least 7 days and were anticipated to survive at least another 24 hours, and who were not in ICU with brain injury. (Other exclusions are documented in Figure 1 of their article.) The 7-day mark was chosen, it appears, on the basis of expert clinical judgment and plausibility. Of the 534 participants enrolled, 398 survived the ICU, and 391 survived the ICU by at least a week to become the cohort.