Chapter 17
Coma and disorders of consciousness

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INTRODUCTION
Severely brain-damaged patients pose major challenges regarding treatment and end-of-life issues. Advances in medical technology increasingly confront physicians, social workers, and lawyers with ethical issues. This situation is dramatically illustrated by the case of Julia Tavalaro, who survived a brain trauma and was transferred to a nursing care center where she was called “the vegetable” for over 6 years, although she was conscious and sensate (Tavalaro and Tayson, 1997). In Italy, the story of Eluana Englaro, a 36-year-old woman who remained unconscious for 17 years after a car accident, became the focus of a court battle between supporters and opponents of euthanasia (Luchetti, 2010).

Stories of this kind have inspired several social, political, and religious groups to emphasize that these patients have rights to be fully considered as human beings by also recognizing their right to die (Table 17.1) (Borthwick, 1995; Velez, 2005). Moreover, important figures in the history of the right-to-die movement (Table 17.2) have provided the background for examining the advancement of clinical decision-making, including when to use or not to use technologies such as ventilators and artificial nutrition and hydration.

Indeed, the invention of the artificial respirator in the 1950s has assisted many patients to sustain their cardiac circulation, who otherwise could not have survived their acute brain damage and coma. This treatment has led to the redefinition of death based on neurologic criteria (i.e., brain death or irreversible coma with absent brainstem reflexes: Laureys, 2005) and to the identification of states of profound paralysis causing pseudocoma (i.e., locked-in syndrome (LIS): Laureys et al., 2005). Nevertheless, the decision to withdraw or withhold such life-sustaining means is controversial and possibly influenced by clinical diagnosis and prognosis.

The vegetative state
In the 1970s patients who awakened from coma – i.e., they opened their eyes spontaneously or after stimulation but remained without communication or behavioral signs of consciousness – were coined as being in a “vegetative state” (VS (Jennett, 2005)) or, as previously called, in “apallic syndrome” or “coma vigil” (Fig. 17.1). The name “vegetative” was chosen to refer to the preserved autonomous nervous functioning in these patients such as sleep–wake rhythm, respiration, digestion, and thermoregulation. The term “persistent” was added to denote that the condition remained present for more than 1 month after the insult. In 1994, a retrospective study of all published cases permitted criteria for the temporal boundaries of irreversibility of this syndrome, hence proposing the term “permanent vegetative state” (The Multi-Society Task Force on PVS, 1994a) (unfortunately, persistent and permanent VS share the common abbreviation of “PVS,” leading to unhelpful confusion).

However, it appears that part of the healthcare, media and lay public continues to feel unease regarding the unintended denigrating “vegetable-like” connotation seemingly intrinsic to the term VS. Therefore, the European Task Force on Disorders of Consciousness recently proposed the alternative name “unresponsive wakefulness syndrome” (UWS) (Laureys et al., 2010). Physicians now may refer to these patients as UWS, a less pejorative and more neutral and descriptive term, referring to patients showing the clinical syndrome of unresponsive unawareness (that is, without response to commands or oriented voluntary movements) in the presence of wakefulness. It is in these cases that the most

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difficult end-of-life issues occur, especially those involving withholding and withdrawal of life-sustaining treatments (Luchetti, 2010; Solarino et al., 2011).

The minimally conscious state

In 2002, the operational criteria for the “minimally conscious state” or MCS were published and recommended by the American Academy of Neurology, separating non-communicative “vegetative” patients from patients showing minimal fluctuating behavioral signs of consciousness (Giacino et al., 2002). Patients in MCS may show some signs declaring awareness, such as visual pursuit, orientation to pain, or nonsystematic command-following, but they are unable to communicate their thoughts or feelings.

We have recently proposed subcategorizing the clinically heterogeneous MCS entity to minimally conscious plus (MCS+) and minimally conscious minus (MCS–) based on the level of complexity of observed behavioral responses (Bruno et al., 2011b). MCS+ was defined by the presence of command-following. In contrast, MCS– patients show only minimal levels of behavioral interaction characterized by the presence of non-reflex movements, for example orientation of noxious stimuli, pursuit eye movements that occur in direct response to moving or salient stimuli, or affective behaviors that occur in contingent relation to relevant environmental

Table 17.1

Locked-in patients’ personal memoirs

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Title (publisher)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julia Tavalaro (1997)</td>
<td>Look up for Yes (Kodansha, New York)</td>
</tr>
<tr>
<td>Philippe and Stéphane Vigand (2000)</td>
<td>Only The Eyes Say Yes (original title: Putain de silence) (LGF – Le Livre de Poche)</td>
</tr>
<tr>
<td>Roland Bouleengier (2001)</td>
<td>De eenzame stille (De Mol)</td>
</tr>
<tr>
<td>Philippe Vigand (2002)</td>
<td>Promenades immobiles (Le Livre de Poche)</td>
</tr>
<tr>
<td>Leatitia Bohn-Derrien (2005)</td>
<td>Je parle: l’extraordinaire retour à la vie d’un Locked-In Syndrome (J.-C. Lattès)</td>
</tr>
<tr>
<td>Roland Bouleengier (2005)</td>
<td>‘Dat andere leven’ Thuis met locked-in (SIG vzw)</td>
</tr>
<tr>
<td>Philippe Prijent (2006)</td>
<td>Emmuré vivant dans mon corps (ABM Editions)</td>
</tr>
<tr>
<td>Jean Busalb (2007)</td>
<td>Vies brisées (J. Do Bentzinger)</td>
</tr>
<tr>
<td>Roland Bouleengier (2007)</td>
<td>‘PAB-geassisteerd leren leven’ De wereld van locked-in (SIG vzw)</td>
</tr>
<tr>
<td>Benoît Duchesne (2008)</td>
<td>Un esprit clair dans une prison de chair (La semaine)</td>
</tr>
<tr>
<td>Roland Bouleengier (2009)</td>
<td>Verlengingen. ‘Overleven als locked-in’ (SIG vzw)</td>
</tr>
<tr>
<td>Bruno Lamarare (2009)</td>
<td>Penser est ma liberté (Donnez un sens à vos voeux)</td>
</tr>
<tr>
<td>Zoubida Touarig (2009)</td>
<td>Le cri du silence (Beaurepaire)</td>
</tr>
<tr>
<td>Jean-Baptiste Courtois (2009)</td>
<td>Noir et blanc (Baudelaire)</td>
</tr>
<tr>
<td>Philippe Vigand (2011)</td>
<td>Légume vert (Anne Carrière)</td>
</tr>
<tr>
<td>Alison Stokes and Kate Allatt (2011)</td>
<td>Running Free: Breaking Out From the Locked-In Syndrome (Accent Press)</td>
</tr>
</tbody>
</table>

Table 17.2

Important figures in the history of the “right-to-die” controversy

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>Diagnosis</th>
<th>Time since injury</th>
<th>Date of death (cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinlan, Karen Ann</td>
<td>United States</td>
<td>Vegetative state</td>
<td>9 years</td>
<td>11 June 1985 (pneumonia)</td>
</tr>
<tr>
<td>Cruzan, Nancy</td>
<td>United States</td>
<td>Vegetative state</td>
<td>7 years</td>
<td>26 December 1990 (end-of-life treatment)</td>
</tr>
<tr>
<td>Schiavo, Terri</td>
<td>United States</td>
<td>Vegetative state</td>
<td>14 years</td>
<td>31 March 2005 (end-of-life treatment)</td>
</tr>
<tr>
<td>Englaro, Eluana</td>
<td>Italy</td>
<td>Vegetative state</td>
<td>17 years</td>
<td>9 February 2009 (end-of-life treatment)</td>
</tr>
</tbody>
</table>
stimuli. Emergence from MCS is defined by the ability of patients to communicate functionally and accurately or use objects in a meaningful way.

The locked-in syndrome

In rare cases of brainstem lesions, patients can fully recover consciousness but remain totally paralyzed and aphasis, in the aptly named “locked-in syndrome” (Laureys et al., 2005). LIS patients are able to communicate only with small vertical eye movements (American Congress of Rehabilitation Medicine, 1995). The difficulty in disentangling reflexive from voluntary responses, the fluctuation of vigilance, and additional cognitive or sensory deficits may lead to a high rate of misdiagnosis not only between UWS/VS and MCS (Andrews et al., 1996; Childs and Mercer, 1996; Schnakers et al., 2009) but also LIS (Bruno et al., 2009). This distinction is important when one considers the extent to which the diagnosis influences decisions about the patients’ care, particularly regarding crucial matters such as pain management (Demertzi et al., 2009) and end-of-life decisions (Demertzi et al., 2011b, 2012).

MANAGING PAIN IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS

As defined by the Multi-Society Task Force on PVS (1994b), “pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that they may emanate endogenously from the depths of human self-perception.” Thus, pain constitutes a conscious experience with a physical (nociception) and a psychologic (suffering) counterpart, suggesting that nociception by itself is not sufficient to cause suffering. Detecting pain in non-communicative patients with disorders of consciousness constitutes a real challenge because patients in UWS/VS and MCS cannot communicate their feelings or experiences either verbally or non-verbally (Laureys and Boly, 2007). This challenge is reflected in whether and how clinicians perceive pain in these patients.

In a European-wide survey, responses were collected from a questionnaire that was distributed during lectures at medical and scientific conferences and meetings. The majority of the interviewed paramedical caregivers (68%) and medical doctors (56%) agreed with the question “Do you think that patients in a UWS/VS can feel pain?” To the question “Do you think that patients in a MCS can feel pain?” nearly all interviewed caregivers answered “yes” (96% of the medical doctors and 97% of the paramedical caregivers) (Demertzi et al., 2009). Considering these results on varying beliefs about pain perception in disorders of consciousness, physicians and healthcare workers’ views on analgesia and symptom management may also be affected. Because nearly half of the doctors surveyed expressed that UWS/VS patients do not feel pain, they could be expected to act accordingly, for instance, by not providing analgesic medication in these patients during medical care or during the dying process after withdrawal of artificial hydration and nutrition (Fins, 2006), the latter on the grounds that these patients do not experience suffering from hunger or thirst (Ahronheim and Gasner, 1990).

Of course, there is a theoretic problem with evaluating the subjective experience of pain and any other conscious perception or thought in another person (Demertzi and Laureys, 2012). At the patient’s bedside, we are limited to evaluating the behavioral responsiveness to pain. If patients never show any signs of voluntary movement in response to noxious stimuli, usually it will be concluded they do not experience pain. However, the absence of a behavioral response cannot be taken as an absolute proof of the absence of consciousness (McQuillen, 1991; Bernat, 1992). Given these limitations of our bedside clinical assessment, information coming from neuroimaging technologies may assist the formulation of a clearer clinical picture.
Neuroimaging studies

Neuroimaging research indicates distinct cerebral activations to painful stimulations in UWS/VS and MCS patients. In healthy volunteers, studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed that nociceptive stimulations induce the activation of neural circuitry called the pain “neuromatrix.” This brain system can be further reduced in a sensory network (encompassing lateral thalamic nuclei, primary, secondary somatosensory, and posterior parietal cortices) and an affective network (encompassing medial thalamus, anterior cingulate, and prefrontal cortices, with the insular cortex playing an intermediate role (Jones et al., 1991; Peyron et al., 2000; Hofbauer et al., 2001).

In a PET study with patients in UWS/VS, our group found that these patients may show cerebral processing of the incoming noxious stimulus (i.e., activation of primary somatosensory areas), but the observed activity was isolated and disconnected from higher-order associative brain areas that are considered necessary for conscious perception of pain (Laureys et al., 2002). In contrast, MCS patients showed brain activation comparable to healthy controls and this activation was spreading to secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices, suggesting preserved capacity of pain experience in these patients (Boly et al., 2008). These neuroimaging data therefore highlight large differences in brain activation between UWS/VS and MCS patients.

Clinical scales

The detection of behavioral signs of nociception at the bedside in patients recovering from coma represents an important medical challenge. Although several scales have been used to assess nociception in non-communicative patients such as with end-stage dementia, newborns and in sedated intensive care patients, no scale was developed to assess pain in patients with disorders of consciousness (Schnakers et al., 2010a, b). We recently proposed the use of the Nociception Coma Scale-Revised (NCS-R) as a standardized and validated tool measuring motor, verbal, and facial expression in response to pain in UWS/VS and MCS patients (Chatelle et al., 2012) (Fig. 17.2).

In order to validate the scale, we compared behavioral changes observed with the NCS-R in noxious (pressure on the nail bed) as well as non-noxious/tactile stimulation (taps on the patient’s shoulder) conditions. We showed that the NCS-R total scores were higher for the noxious stimulation condition as compared to non-noxious/tactile stimulation, suggesting the NCS-R is sensitive for assessing responses to noxious stimulation. Moreover, the cut-off value of the NCS-R total score which differentiates noxious versus non-noxious stimulation is 4, therefore suggesting the initiation of analgesic treatment in patients.

**ETHICAL CHALLENGES IN END-OF-LIFE CARE**

Disorders of consciousness may not only pose medical challenges but in some cases they require the mediation of legal authorities in order to regulate end-of-life decisions (Demertzi et al., 2011a). UWS/VS and MCS patients represent a difficult group, ethically, for surrogate decision-making. Should we continue the patient’s treatment at all costs? Should we treat cardiac arrest or kidney failure or pneumonia in these patients? The medical community needs policies to reach better internal agreement within the professional network and effective communication with patient communities and their families (Jox et al., 2012).

**Survey data**

The controversies around the clinical management at the end of life in patients with disorders of consciousness were reflected in a recent European survey (Demertzi et al., 2011b). For chronic UWS/VS (more than 1 year), 66% of healthcare professionals agreed to withdraw
treatment whereas only 28% agreed to do so for MCS patients. Additionally, most clinicians wished not to be kept alive if they imagined themselves in a chronic UWS/VS (82%) and a similar proportion (67%) agreed so if they imagined themselves in a chronic MCS. The distinction between personal preferences with private consequences (i.e., “I would like to be kept alive if I were...”) and more objective statements of societal significance (i.e., “It is acceptable to stop treatment in...”) are in accordance with previous findings showing that the majority of surveyed physicians and nurses would refuse treatment for themselves more than for patients (Gillick et al., 1993).

In our survey, we also found that end-of-life decisions are not always governed by clinical circumstances but rather physicians’ characteristics (i.e., age, religion, and geographic region). Geographic differences as well as religious background were the variables that consistently predicted end-of-life statements. Residents from northern and central Europe, as compared to southern Europeans, were more likely to agree with medically assisted nutrition and hydration withdrawal in chronic UWS/VS (Fig. 17.3), whereas religious respondents, older respondents, and women were less likely to find it acceptable.

**Surrogate decision-making**

When the clinical condition of a patient is stabilized and determined to be irreversible, decisions about limiting artificial nutrition and hydration may be raised. In some jurisdictions, decisions for treatment limitation by restricting hydration and nutrition require referring the matter to the courts, though this requirement varies widely among countries. If end-of-life wishes have not been earlier expressed in the form of an advanced directive (i.e., by means of a written legal statement completed by a competent person in anticipation of her/his future incompetence that allow decisions to be conveyed about end-of-life care ahead of time), then a lawful surrogate decision-maker is required to take decisions for the patient’s clinical management.

The surrogate decision-maker should first attempt to follow the wishes of the patient as they were expressed before the accident and based on the patient’s history and personal values. Physicians and surrogate decision-makers should explore the conditions of these statements to decide whether or not this information is relevant and reliable. When this is not possible, decisions should rely on more objective markers that determine the patient’s best interest, such as the likelihood of recovery, pain management, and impact on family (Bernat, 2002, 2004).

**Guidelines**

From a bioethical standpoint, withdrawing artificial nutrition and hydration is comparable to withdrawing mechanic ventilation, even if emotionally and psychologically these two actions may be perceived differently (Laureys, 2005). Despite the controversy as to whether artificial nutrition and hydration constitutes medical treatment (Bernat and Beresford, 2006), most of the medical community agrees that it is a medical therapy which can be refused by patients and lawful surrogate decision-makers (Steinbrook and Lo, 1988). Similarly, a national survey of Italian physicians’ attitudes towards end-of-life decisions showed that 61% of the doctors questioned considered tube feeding to be a medical therapy and 66% believed that withdrawal of assisted nutrition and hydration might be appropriate depending on the patient’s wishes (Solarino et al., 2011).

Such decisions in unconscious patients are only reasonable when the medical situation is considered as permanent and irreversible (Royal College of Physicians, 2003). In 1994, the Multi-Society Task Force on PVS defined the temporal criteria for irreversibility and currently states that if no recovery is observed within 3 months after a non-traumatic or 12 months after a traumatic accident, the condition of the patient can be
denoted as permanent (The Multi-Society Task Force on PVS, 1994b).

For these problematic cases, relating to the value of life for patients who are conscious but not terminally ill, there are few ethical and legal guidelines about end-of-life treatment. Therefore, it is difficult to establish with any degree of certainty at what point after a brain injury this condition becomes irreversible and more longitudinal data are needed to confirm the criteria for, and timing of, realistic prognosis for recovery.

For example, the case of Wendland, a chronic traumatic patient in MCS with no advance directive, raised the ethical question on end of life in non-communicative patients. The court was asked to rule on his level of treatment. His wife claimed that, during informal conversations about end-of-life care with her and their children, her husband said that he never wished to live in such a state and that he would want his gastrostomy feeding tube removed to allow him to die. By contrast, Wendland’s mother wished to maintain the gastrostomy tube feedings to keep him alive, claiming that he would wish to live under these circumstances. California’s highest court mandated continued treatment (Lo et al., 2002).

Similarly, a recent article described the decision from the Court of Protection in England to rule on the issue of a patient in MCS where the family asked to stop the assisted nutrition and hydration. The judge concluded that the patient’s treatment must continue (Huxtable, 2012). These decisions raise substantive and evidential interrogations regarding where the burden of proof should lie and what standard of proof should be required when decisions are to be made about the destinies of patients who are “minimally” conscious but unable to communicate and express their wishes.

**ASSESSING QUALITY OF LIFE IN SEVERELY DEPENDENT PATIENTS**

It is usually easy to evaluate a third person’s situation by directly asking her/him what it feels like to be in a particular condition. In the field of neurology and neurocritical care, studies on quality of life (QoL) have been relatively slow to develop, mainly due to the limited means of communicating with severely brain-damaged patients (Murrell, 1999). Specifically for UWS/VS or MCS patients, QoL information cannot be acquired because by definition these patients are unable to communicate. Hence, qualitative estimations can only be inferred by observing behavioral output or by empathic mechanisms acting as if one is “walking in someone else’s shoes” (Demertz et al., 2013a).

For example, in a recent European survey, healthcare professionals were asked to affirm their opinions on what it is like to be in a UWS/VS and an MCS. The majority found that chronic UWS/VS is worse than death more so from the perspective of the family (80%) compared to that of the patient (55%). Conversely, MCS was considered worse than UWS/VS for the patients in 54% and for their families in 42% of the sample (Demertz et al., 2011b).

Previously Dennett (1976) similarly reported that nearly 90% regarded UWS/VS survival as worse than death, a few commenting that the question was irrelevant for the patient, whereas 95% would consider that the families would consider it worse. From these data, it has been argued that the presence of consciousness does not necessarily assure a better QoL and, thus, it may not be in patients’ best interest to continue living under unsatisfactory conditions (Kahane and Savulescu, 2009). To date, however, there is no generally accepted definition as to what health-related QoL refers to. It can be seen as the comparison between the patient’s expectations of health and her/his experience of it (Carr et al., 2001).

Autonomy and physical functioning have long been seen as the prerequisites of a “life worth living” (Chin et al., 1999). The arising question is what the consequences are for people with extreme motor impairment, in which the probability for regaining autonomy in daily life is very limited. Therefore, is life worth living after severe traumatic brain injury? As the assessment of QoL in UWS/VS and MCS patients remains difficult, we recently decided to assess the degree of satisfaction of severely disabled patients – patients in LIS.

Collaborating with the French Association for Locked-In Syndrome, we recently reported on the overall QoL of 65 chronic LIS patients. Participants were asked to complete a structured questionnaire aided by their proxies (Bruno et al., 2011a). We used the French postal version of the Reintegration to Normal Living Index to evaluate the degree to which a patient has been able to return to a normal life (Wood-Dauphinee and Williams, 1987, Daneski et al., 2003). The overall QoL was rated by means of the Anamnestic Comparative Self-Assessment (ACSA: Bernheim, 1999), whose biographic +5 and −5 scale anchors were the patients’ memories of the best period in their life before LIS (+5) and their worst period ever (−5). Information about sociodemographic (age, gender, educational level, place and condition of living, religiosity, net monthly household income), clinical (etiology and duration of LIS, level of speech production, and motor recovery) and QoL variables was also collected.

Results showed that 51% of respondents self-reported severe restrictions in community reintegration in line with previous studies in paraplegia following spinal cord injury (May and Warren, 2002; Tonack et al., 2008). Only 21% were engaged in most of the daily activities that they
considered important. The majority (82%) were comfortable with personal relationships and only a minority were dissatisfied with their participation in recreational (12%) or social (40%) activities. Forty-seven patients professed happiness (median ACSA +3) and 18 unhappiness (median ACSA −4). In the unhappy group, depression, suicidal ideas, consideration or wish for euthanasia, and the wish not to be resuscitated in case of cardiac arrest were reported significantly more frequently (28%).

The variables associated with unhappiness were dissatisfaction with mobility in the community, with recreational activities, and with the capacity to deal with life events. Shorter time in LIS, anxiety, and non-recovery of speech production were also associated with unhappiness. Nevertheless, the majority (72%) of our sample professed “good” QoL (ACSA rating ≥ 0, median +3). Our results are in line with the notion that patients with severe disabilities may report a good QoL despite being socially isolated or having major difficulties in activities of daily living (Post et al., 1998; Albrecht and Devlieger, 1999).

The self-reported happiness may suggest that these patients have succeeded in adapting to their condition of extreme physical disability (Nizzi et al., 2012). According to Cummins’ theory of subjective wellbeing, patients’ homeostatic resources may have overcome even the formidable challenge of LIS (Cummins, 2003). Therefore, our findings highlight the strength of homeostatic processes of adaptation to chronic (often definitive) extreme disability. The “happy” subgroup of LIS survivors may indeed be those respondents capable of high flexibility and plasticity who have fully succeeded in recalibrating, reprioritizing, and reorienting their needs and values. In that respect, low raters cope poorly because they cannot shed the needs and values from their previous life. Because such an adaptation process is lengthy, this hypothesis is consistent with the observed positive association of QoL with duration of time in LIS, corroborating previous studies on QoL in spinal cord injury patients (Calmels et al., 2003; Tonack et al., 2008).

CONCLUSIONS

Patients with disorders of consciousness pose medical, scientific, and ethical challenges. The evaluation of pain, end-of-life preferences, and consequently the assessment of patients’ quality of life is not straightforward. In many cases, clinicians and researchers are faced with confounding factors that may lead them to underestimate a patient’s mental and cognitive capacities, such as aphasia syndromes (Majerus et al., 2009). Also, negative results in clinical trials and research activation protocols (Monti et al., 2010) do not necessarily imply absent cognitive processes in these patients.

Studies with neuroimaging techniques during resting conditions, while patients do not need to perform any specific task, may overcome these issues (Heine et al., 2012). More specifically, with functional neuroimaging we now know that UWS/VS patients preserve wakefulness networks of brainstem and basal forebrain but the cerebral networks accounting for external perceptual awareness and internal self-related mentation are disrupted. By contrast, patients in MCS+ who show non-reflex behaviors are characterized by right-lateralized recovery of the external awareness network. Similarly, patients who evolve to MCS+ and respond to commands recover the dominant left-lateralized language network (Demertzi et al., 2013b). Such efforts are expected to lead to a more accurate understanding of individual patients’ cognitive abilities or even provide prognostic indicators. In terms of treatment planning, patients with disorders of consciousness are now offered the possibility to express their preferences by means of brain–computer interfaces, either fMRI-based (Sorger et al., 2012) or using electrophysiology signals (Lule et al., 2013). Such advances are necessarily accompanied by legitimate neuroscientific and ethical queries on the medical implementations of this new knowledge.

REFERENCES