REVIEW ARTICLE

Movements in Brain Death: A Systematic Review

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ABSTRACT: Brain death is the irreversible lost of function of the brain including the brainstem. The presence of spontaneous or reflex movements constitutes a challenge for the neurological determination of death. We reviewed historical aspects and practical implications of the presence of spontaneous or reflex movements in individuals with brain death and postulated pathophysiological mechanisms. We identified and reviewed 131 articles on movements in individuals with confirmed diagnosis of brain death using Medline from January 1960 until December 2007, using 'brain death' or 'cerebral death' and 'movements' or 'spinal reflex' as search terms. There was no previous systematic review of the literature on this topic. Plantar withdrawal responses, muscle stretch reflexes, abdominal contractions, Lazarus's sign, respiratory-like movements, among others were described. For the most part, these movements have been considered to be spinal reflexes. These movements are present in as many as 40-50% of heart-beating cadavers. Although limited information is available on the determinants and pathophysiological mechanisms of spinal reflexes, clinicians and health care providers should be aware of them and that they do not preclude the diagnosis of brain death or organ transplantation.

RÉSUMÉ: Mouvements et mort cérébrale : revue systématique. La mort cérébrale est une perte de fonction irréversible du cerveau et du tronc cérébral. La présence de mouvements spontanés ou réflexes constitue un défi lors de la détermination neurologique de la mort. Nous avons révisé les aspects historiques et les implications pratiques de la présence de mouvements spontanés ou réflexes chez les individus en état de mort cérébrale et nous postulons des mécanismes physiopathologiques pour les expliquer. Nous avons révisé 131 articles identifiés dans Medline, qui avaient été publiés entre janvier 1960 et décembre 2007 et qui portaient sur la présence de mouvements chez des individus dont le diagnostic de mort cérébrale était confirmé. Les mots clés utilisés étaient les suivants : mort cérébrale, mouvements, réflexe spinal. Nous n'avons trouvé aucune revue systématique de la littérature sur ce sujet. Des réflexes de retrait à la stimulation plantaire douloureuse, des réflexes ostéo-tendineux, des contractions abdominales, le signe de Lazare, des mouvements ressemblant à des mouvements respiratoires ont été décrits. En général, ces mouvements ont été considérés comme des réflexes spinaux. Ces mouvements sont présents chez près de 40 à 50% des cadavres dont le cœur bat toujours. Bien que l'information disponible sur les déterminants et les mécanismes physiopathologiques des réflexes spinaux soit limitée, les cliniciens et les soignants devraient connaître leur existence et savoir qu'ils ne sont pas incompatibles avec un diagnostic de mort cérébrale et ne constituent pas un obstacle à la transplantation d'organes.

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Historical Aspects

For centuries physicians, philosophers and various writers have written about death and its many peculiarities, including movements of the dead. One of the very first was René Descartes, who mentioned, that the heads, as well as the bodies of dead animals continued moving post-decapitation (Discourse on the Method, 1637). There have been reports of body movements in beheaded people during the French Revolution. Renaissance paintings illustrate decapitations of the time with the decapitated bodies standing upright. "Fra Giovanni da Fiesole" (Beato Angélico, 1395-1455) painting entitled "The decapitation of Saint Cosmas and Saint Damian" (Louvre Museum, Paris) is an example of the decapitation scenes.

Regnard and Loye (1887), physicians during the French Revolution, wrote about jaw contraction and eyelid movements in a decapitated head, although no reflex movements in the body were appreciated[1]. On further examination of the head severed from the body, it was noticed that although the guillotine blade had slashed through the fourth cervical vertebra; the heart kept beating for an hour after decapitation. According to Alister Kershaw in A History of the Guillotine, a French physiologist named Pierre Jean Cabanis was given the task in 1795 to determine if the victims of the guillotine were conscious after beheading. There were also tales of beheaded bodies standing up

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after the fall of the guillotine blade and walking around before finally collapsing[2]. The mechanism behind these phenomena was not described and as such, the mysteries surrounding movements in the dead had continued to bewilder people across borders and civilizations.

Concept of Brain Death

Although by definition the diagnosis of brain death (BD) requires the irreversible loss of cerebral function, including the brainstem (AAN practice parameters, 1995)[3], it appears that all functions are not immediately lost. Several functions including temperature regulation, hypothalamic-pituitary-adrenal axis function, as well as spinal reflexes can be maintained for up to several hours/days. With the advent of donor organ transplantation, the need for a well-established and reproducible BD diagnostic criteria emerged. The first of these criteria were developed in 1968 by the Harvard Medical School Committee. However, these criteria did not allow for any spontaneous or reflex movements (SRMs) (Ad Hoc Committee of the Harvard Medical School 1968)[4]. The criteria included deep, unresponsive coma, with absent brainstem reflexes and apnea. The Canadian guidelines for brain death declaration were first published in 1981; these allowed for the presence of spinal reflexes[5]. Further refinements followed, again allowing for spinal reflexes in the USA, the UK and Canada[4-7]. Most guidelines also preclude the presence of hypothermia, central nervous system (CNS) depressant toxins/drugs, metabolic derangements and neuromuscular blocking agents.

The concept of BD and its correct diagnosis have gained importance with organ transplantations[8]. However, data from a survey published in 1989 revealed that only 35% of health professionals (76 physicians and 80 nurses) involved in organ procurement for transplantation was able to correctly diagnose BD[9]. This also reflects the lack of a systematic approach or well-defined diagnostic criteria of BD.

The word ‘patient’, after coming to the diagnosis of BD, does not seem appropriate as ‘patient’ implies a person who is alive. Further, in countries where BD is equivalent to death of the individual, the patient has lost his legal personhood. Since brain dead victims are "legally dead" in Canada, we prefer to use ‘heart-beating cadaver’ (HBC) instead of ‘patient’. In a recent review and case report[10], the authors also acknowledged problems with terms for “movements” in BD nomenclature, suggesting that stimulus-provoked movements be referred to as BD-associated reflexes, while spontaneous movements as BD-associated automatisms.

Awareness of the clinical criteria for BD diagnosis and its legal and practical implications are of utmost importance. We have, therefore examined the nature, frequency, and pathophysiological mechanisms of SRMs in BD. A summary of historical perspective, animal studies, and evidence from clinical series to well-documented case-reports is provided.

Methods

We searched Medline using index terms (‘brain death’ OR ‘cerebral death’ AND ‘movements’ OR ‘spinal reflexes’ limited to studies from January 1960 until December 2007. Studies were included if they reported the presence of spontaneous or reflex movements in a HBC with confirmed BD as described in the AAN guidelines. Specifically, there has to be a clear documentation of i) unresponsiveness, ii) absent brainstem reflexes, and iii) apnea and/or complementary studies revealing the absence of cerebral blood flow. We included case reports if the diagnosis of BD was adequately described in the methods section or specified diagnostic criteria. We also evaluated the references of the retrieved articles. Titles and abstracts of identified published articles were reviewed independently (by GS and VB) to determine the relevance of the articles. Each citation was classified as 'inclusion' or 'exclusion'. For feasibility reasons, no attempts were made to directly contact authors of published papers.

In case of disagreement between the two reviewers, consensus was reached to solve the disagreement. After this, excluded citations were no longer considered.

Figure: *Illustration of the decapitation of Saint Cosmas and Saint Damian. Saint Cosmas and Saint Damian were twin brothers born in Arabia, who became skilled doctors. Known as the "moneyless", they never accepted money for their services, but offered them in the spirit of charity. When the persecution under Diocletian broke out, their very prominence rendered them marked objects of persecution. Being apprehended by order of Lysias, governor of Cilicia, they were arrested, tortured, and beheaded in the year 283. Fra Giovanni da Fiesole (Beato Angélico, 1395-1455) illustrated decapitated bodies maintaining the postural tone as represented by the bodies standing upright. The picture is currently exhibited at Louvre Museum, Paris.*

Results

One hundred and thirty one articles were identified in the systematic review using ‘brain death’ and ‘movements’ or ‘spinal reflex’. We found four cohort studies (Level of evidence: B), while the remaining were case series or case reports (Level of Evidence: C). We found no randomized clinical trials (Level of evidence: A). Articles were classified in evidence from ‘animal studies’, ‘case reports/case-series’, cohort studies’, and articles providing some evidence on the underlying pathophysiological mechanisms.

Clinical evidence from animal studies

Walking or stepwise locomotion, although complex in its intricate coordination of activation of several agonist antagonist muscles, is quite simple in its rhythmic and alternating movements of the appendages. The basic control of the repetitive quality of stepwise locomotion allows it to be controlled automatically by relatively lower levels of the nervous system without intervention from higher cortical centers. Evidence from animal studies in both vertebrates and invertebrates have shown that in basic neural oscillators controlling reflex behaviors such as stepwise locomotion are controlled within the spinal cord. Several insights into the control of stepwise locomotion were made in the early 1900s when it was initially found that removing the cerebral hemispheres of dogs did not abolish walking. In 1911, Thomas Graham Brown showed stepwise movements in both cats and dogs elicited after complete transection of the spinal cord[11]. The "half center hypothesis" is supported by spinal cord centers activating flexor motoneurons that inhibited the activation of the spinal cord centers activating extensor motoneurons, and vice-versa[12]. After the spinal cord was transected cats exhibited stepwise locomotor activity after the administration of levodopa and the application of brief trains of electrical stimuli applied to smaller diameter cutaneous and muscle afferents. More coordinated walking type movements were seen, with adrenergic agents. The aforementioned evidence suggests that in the absence of cortical inhibitory and modulatory afferents to these spinal cord centers could allow for activation of these basic spinal cord programs, causing the reflex movements commonly seen in brain dead humans[13].

Clinical evidence from case reports, case series and cohort studies

The relative paucity of studies on movements in BD as well as key differences among these studies makes accurate summarization of the literature a daunting task. Direct comparison of the studies is limited by several factors, including: 1) discrepancies in the BD diagnostic criteria; 2) the diversity of the population studied; 3) differences in collection of data elements; 4) methodological differences (prospective vs. retrospective); and 5) disparities in the objectives of the study.

Table 1 summarizes characteristics and the frequency of SRM's in cohort studies including more than 50 HBCs.

In his retrospective study, Ivan showed deep tendon reflexes in 35% of the BD patients, plantar withdrawal in 35%, plantar flexor responses in 60%, and abdominal reflexes in 40% of individuals[13]. He also found neck-arm flexion in 25%, neck-hip flexion in 45%, and neck abdominal reflex in 75%. These observations suggest that Ivan only took simple reflexes into account, and did not study more complex movements[14].

Jorgensen's later study on movements in the BD went a little further and looked at more complex movements, emphasizing the persistence or regaining of spinal reflex activity after BD[15]. In his study of 63 individuals, he found lower limb withdrawal responses in 50 of the cases, deep tendon reflexes in the upper extremities in 31, and lower extremities deep tendon reflexes in 24 BD subjects. In this seminal work, Jorgensen also introduced the term "extension-pronation arm reflex" after he found extension and pronation of the arm and forearm in response to cutaneous stimulation in 21 of the subjects. He is also credited with the term "spinal man", which he introduced after he found

Table 1: Summary of cohort studies on SRMs in HBCs

Study	Study Size	Study design	Standardized protocol to elicit SRMs	AAN Criteria for BD	Mean age	Most common etiology of BD (%)	n (%) with SRM's	Most common movement reported
Ivan, 1973	52	Retrospective	No	No*	NA	Traumatic brain injury (54)	39 (75)	- Plantar flexion response and abdominal reflexes
Jorgensen, 1973	63	Retrospective	No	No†	NA	Traumatic brain injury (44)	50 (79)	- Triple flexion response and "extension and pronation" of the arm and forearm
Dosemeci, 2004	134	Prospective	Yes	Yes	39.1	ICH (31)	18 (13.4)	- "finger and toe jerk"
Saposnik, 2005	107	Prospective	Yes	Yes	42.1	ICH (46)	47 (43.9)	- Undulating toe flexion and triple flexion response
All	356	NA	NA	NA	NA	TBI & ICH	154 (43.3)	NA

NA=non-available or non-applicable. ICH= intraberebral hemorrhage, TBI= traumatic brain injury; * All individuals had a flat EEG for 30 minutes, respiratory arrest, and absence of brainstem reflexes; † All HBC fulfilled the following criteria: cessation of the brain functions, demonstration of no cortical activity in the electroencephalogram recorded during 30 minutes, no cranial nerve reflexes, including no spontaneous respiratory movement and no spontaneous maintenance of systemic blood pressure, and neither supratentorial- nor infratentorial circulation on serial angiography performed twice at an interval of more than 20 minutes.

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that HBCs often retained, or regained, spinal reflex activity after BD. He observed that those who regained spinal reflex activity did so within six hours of BD diagnosis documented by cerebral angiography. He also observed that the delayed appearance of spinal reflexes was invariably associated with severe arterial hypotension. Jorgensen further extended these findings indicating that "when there is no access to electro-encephalography or cerebral angiography, the presence of unilateral extension-pronation reflex of the upper limb can be used as an indication of BD of any etiology".

Conci et al observed 25 subjects deemed to be brain dead according to Italian criteria including absence of brainstem reflexes, isoelectric EEG and positive apnea test for greater than two minutes during kidney removal for transplantation[16]. The authors found that in 60% of the subjects abdominal muscle contractions were present. Muscle contractions were present after the parietal peritoneum was cut. In 24% of the HBCs sudden changes in blood pressure and heart rate were also noticed on first incision; but there was no movement during bowel manipulation. These responses, according to the authors, were related to persistence of spinal reflexes during the ablation period.

Our group prospectively completed a feasibility study including 38 HBC who fulfilled the AAN criteria for BD to assess a standardized protocol, designed specifically to elicit reflex movements (before or during the apnea test), including: 1) painful stimuli to the sternum, the four limbs, and supra-orbital area; 2) neck flexion; 3) tactile stimuli to the palmar and plantar surfaces; and 4) elevation of the four limbs. We found spontaneous or reflex movements in 15 (39%)[17].

More recently, our group conducted a multicentre study including 107 HBCs fulfilling AAN criteria for BD. Forty-seven (44%) had spontaneous or reflex movements[18]. There were no significant differences in age, sex, and cause of BD between individuals with and without involuntary movements. The most common movements were the undulating toe reflex and the triple flexion response. Movements were more common in HBCs with intracerebral hemorrhage (51%), and less common in those with anoxic-ischemic encephalopathy (11%). A summary of the frequencies of the various documented movements in BD are summarized in Table 2. Twelve HBCs (26%) had more than one type of movement.

Another series by Han and colleagues[19] investigated SRMs in a sample of 26 Korean HBCs, finding that five (19.2%) exhibited reflex movements such as the pronation-extension reflex, abdominal reflex, flexion reflex, the Lazarus sign, and repetitive leg movements mimicking periodic leg movement during sleep. All HBCs fulfilled the Korean and AAN Criteria for BD.

Döşemeci and colleagues[20] reported a series of 134 HBCs in which BD was established clinically and including apnea test. Spinal reflex movements were observed in 18 (13.4%) HBCs. Multiple occurrences of 'Lazarus sign' was observed in two HBCs during apnea testing, oculocephalic testing, after painful stimulus, and after removal of the ventilator. The other reflex movements observed included finger and toe jerks, extension at arms and shoulders, and flexion of arms and feet.

The first documented report of the "Lazarus' sign" came from Mandel and colleagues in 1982 in a 28 year-old man diagnosed with BD[21]. The authors described spontaneous movement of the arms with flexed elbows and hands held together in a praying position, followed by hand separation with subsequent arms falling to the sides of the torso. The legs also moved in walking-like movements.

Table 2: Spontaneous and reflex movements (SRMs) described in BD

SRMs
Flexor/ extensor plantar responses
Triple flexion response
Abdominal reflex
Cremasteric reflex
Tonic-neck reflexes
Isolated jerks of the upper extremities
Unilateral extension-pronation movements
Asymmetric ophisthotonic posturing of trunk
"Undulating toe flexion sign"
Myoclonus
"Lazarus sign"
Respiratory-like movements
Quadriceps contraction
Eye opening response
Leg movements mimicking periodic leg movement
Facial myokymia

Later, Ropper described 'Lazarus sign' in five HBCs whose ventilators were disconnected[22]. The movements included shoulder adduction, bringing both arms to the chest, moving the hands to the neck, sometimes crossing and touching each other, and then finally falling to the bed. In two HBCs, passive flexion of the neck elicited a jerk that raised the four limbs off the bed. Dystonic posturing of the fingers and hands were also reported. These movements lasted for only a few seconds. There have been several reports of Lazarus' sign elicited by neck flexion or removal of respiratory support[23-30] or during non-hypoxic conditions[31,32]. Lower extremity movements have also been documented, in addition to trunk flexion[32] and shallow and irregular respiratory movements[24,26].

Other authors described a slow flexion/extension movement of the toes, coined "the undulating toe flexion reflex"[33]. The authors reported three cases that fulfilled the clinical criteria of BD, including EEG and transcranial Doppler (TCD). This movement was either spontaneous or induced by tactile or noxious plantar stimulation. The authors attributed this movement to a spinal mechanism since there was no cerebral or brainstem activity.

Another report is by Santamaria and colleagues who described a BD HBC with either spontaneous or elicited left eyelid opening and closing that persisted for nine days before cardiac arrest[34]. Diagnosis of BD was supported by somatosensory evoked potentials and technetium-99-m-cerebral gammagraphy.

Other documented movements in HBCs include spontaneous low frequency (<6/min) respiratory-like movements when disconnected from the ventilator or when the ventilator was connected with a continuous positive airway pressure of between 4-14 cm H_2O[35]. This was observed in a HBC with anoxic encephalopathy with autopsy proven bilateral uncal and tonsillar herniation, and severe hypoxic ischemic injury to the cerebral cortex, brainstem and spinal cord. Others reported intermittent dystonic posturing of the head and neck with head turning from side to side when nociceptive stimuli were applied to the upper limbs[36,37], as well as decerebrate-like posturing produced by the application of noxious stimuli to arms, thorax, or abdomen[38]. A brain scintigraphy and a transcranial doppler sonography were performed, confirming loss of perfusion in all supratentorial and infratentorial areas.

Our group also observed the presence of facial myokymia in a 54-year-old HBC who fulfilled the AAN criteria for BD following a severe pontocerebellar hemorrhage[39]. Although there was no other facial or limb movements present, intermittent undulating muscle contractions of the left cheek were observed. Brain death diagnosis was also supported by isoelectric EEG and the apnea testing. Interestingly, other authors[40] examined the orbicularis oculi reflex in three HBCs and found that the peripheral nerve conduction in the subjects was intact, but both the early and late components of the reflex were absent bilaterally. Haupt also studied the peripheral nerve conduction in nine HBCs with evoked potentials, blink reflexes and EMG[41] suggesting that facial myokymia in BD may be explained by muscle denervation.

Other uncommon movements include upper and lower facial movements induced by cold water irrigation of the tympanic membranes, eyelid and tongue myoclonus, and spinal myoclonus[42]. However, these are all anecdotal reports and the presence of facial movements precludes the diagnosis of BD.

de Freitas and colleagues[43] reported complex spinal reflexes during transcranial Doppler ultrasound examination in 2.5% of the 161 HBCs examined. TCD studies revealed vertebro-basilar circulatory arrest in all of the patients with complex spinal reflexes. The authors concluded that hypotension and mechanical stimulation play an important role in the pathophysiology of complex spinal reflexes in BD, which are not exclusively seen in terminal hypoxia. Bohatyrewicz and colleagues[44] report a case with spontaneous jerking movements of the lower limbs and clonic movements of the neck muscles secondary to painful stimuli in a HBC with cerebral Dopplers showing circulatory arrest.

The video on-line illustrates the presence of some spontaneous or reflex movements in BD, including: jerks of the upper limb (segment 1), undulating toe flexion reflex (segment 2), triple flexion response (segment 3), left facial myokymia (segment 4), and Lazarus sign (segment 5). Permission was obtained from the next of kin in all cases.

Proposed Pathophysiology of SRM in BD

Although the pathophysiological basis of SRM in BD has remained speculative, several mechanisms have been proposed. It has been postulated the hypoxic stimulation of neurons in the cervical spinal cord isolated from rostral brain areas is a trigger of movements. This is supported by the presence of SRMs after removal of respirator support, during apnea testing, or on instances of arterial hypotension[24,26,31]. Other mechanisms include mechanically induced movements through passive neck flexion and noxious stimuli as reported in the Lazarus sign[25,27].

Dequin and colleagues proposed that these complex movements were the result of mechanical extension of the spinal roots, direct compression of the spinal cord, or the sensory input stimuli[28].

A myriad of neuronal interconnections or neuronal networks, present in the spinal cord have been referred to as "central generators" and are thought to be involved in the generation of some of the SRMs described in BD[45,46]. Distal motor control of the extremities is mediated predominantly by the corticospinal and rubrospinal tracts located in the spinal lateral funiculus. Muscle tone and posture control, synergistic whole limb movement, and spatial orientation of the body and head are mediated more by the vestibulospinal and reticulospinal tracts located more ventrally in the spinal white matter. These tracts as well as the central generators, are thought to be inhibited by supraspinal glycinergic neurotransmission and disconnection from this inhibition may increase excitability at the spinal level, allowing for the occurrence of SRMs[46]. Rhythmic motor patterns are also another plausible mechanism. We can only propose these as possible mechanisms to explain SRMs; unfortunately, there are no well-documented human studies demonstrating these phenomena.

Practical Implications

In the past, death implied immobility. However, the criteria of BD have evolved as a result of increasing scientific evidence and legal and ethical requirements. As an example, according to the initial Harvard Criteria for diagnosing BD, the presence of spinal or cephalic reflexes invalidated the diagnosis. In the AAN guidelines, the presence of spinal reflexes does not preclude the BD diagnosis. The occurrence of movements in HBCs sometimes causes confusion among caregivers and family members, who may question the very diagnosis, and ultimately delay organ procurement for transplantation. A patient fulfilling the criteria for BD ultimately succumbs to cardiac arrest, which usually occurs within a few days following the diagnosis[47]. Further confirmatory testing with EEG, evoked potentials, transcranial Doppler, cerebral angiography and technetium-99-m-cerebral gammagraphy may be required to support the diagnosis and provides further evidence for yet undescribed SRMs in BD. Physicians and health personnel caring for HBCs should be aware of the potential occurrence of SRMs and should also be careful when interpreting them. Explanations should be given to families in order to prevent undue fraught and distress.

Our work has some limitations that deserve further comments. First, the heterogeneity of the study designs may limit a thoughtful analysis of the frequency of SRMs. Second, several studies were published prior to the widely accepted AAN practice parameters for determining BD in adults. However, we only included studies that provide a detailed description of the clinical status and/or evidence supported by complimentary studies. Third, although we did complete an extensive literature

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search using a systematic approach; we were unable to capture unpublished studies or articles published in non-indexed medical journals. Despite these limitations, our work provides a comprehensive review in the understanding of SMRs in BD.

Conclusions

Brain death is a clinical diagnosis that requires - a) absence of cortical functions and brainstem reflexes; and b) irreversibility of the condition. Although spontaneous and reflex spinal movements may be present during the first 24 hours, they do not invalidate the diagnosis. The nature of these movements may be elucidated via electrophysiological, functional imaging, or blood flow studies, leading in future to the development of a standardized protocol.

Given the myriad of practical and legal implications revolving around the diagnosis of BD, our purpose is to alert the health care community about the various types of movements that can be accepted in these circumstances without invalidating the diagnosis.

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Legends for On-line Video

Segment 1- "Jerks of the upper limb": represents jerks of low amplitude affecting the left thumb.

Segment 2- "Undulating toe flexion reflex": sequential brief plantar flexion of the toes.

Segment 3- "Triple flexion response": obtained with tactile stimulation that elicits a flexion moment at the hip and knee and ankle.

Segment 4- "facial myokymia": vermicular facial movements on the left cheek in groups of 3 to 5 twitches lasting for 5 seconds.

Segment 5- "Lazarus sign": sequence of complex movements on passive flexion of the neck. Both upper limbs are raised while there is flexion of the left arm at the elbow. An internal rotation, adduction of the shoulders and pronation of the forearms can be noticed. There is dystonic-like posturing of the hands with extension and abduction of the fingers. A few seconds later, the hands proceed down to the lower abdomen.

At the end, the videotape shows cervical-tonic reflex.