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General Anesthesia Research

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General Anesthesia Research

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Preface to the Series

Experimental life sciences have two basic foundations: concepts and tools. The *Neuromethods* series focuses on the tools and techniques unique to the investigation of the nervous system and excitable cells. It will not, however, shortchange the concept side of things as care has been taken to integrate these tools within the context of the concepts and questions under investigation. In this way, the series is unique in that it not only collects protocols but also includes theoretical background information and critiques which led to the methods and their development. Thus, it gives the reader a better understanding of the origin of the techniques and their potential future development. The *Neuromethods* publishing program strikes a balance between recent and exciting developments like those concerning new animal models of disease, imaging, *in vivo* methods, and more established techniques, including, for example, immunocytochemistry and electrophysiological technologies. New trainees in neurosciences still need a sound footing in these older methods in order to apply a critical approach to their results.

Under the guidance of its founders, Alan Boulton and Glen Baker, the *Neuromethods* series has been a success since its first volume published through Humana Press in 1985. The series continues to flourish through many changes over the years. It is now published under the umbrella of Springer Protocols. While methods involving brain research have changed a lot since the series started, the publishing environment and technology have changed even more radically. Neuromethods has the distinct layout and style of the Springer Protocols program, designed specifically for readability and ease of reference in a laboratory setting.

The careful application of methods is potentially the most important step in the process of scientific inquiry. In the past, new methodologies led the way in developing new disciplines in the biological and medical sciences. For example, Physiology emerged out of Anatomy in the 19th century by harnessing new methods based on the newly discovered phenomenon of electricity. Nowadays, the relationships between disciplines and methods are more complex. Methods are now widely shared between disciplines and research areas. New developments in electronic publishing make it possible for scientists that encounter new methods to quickly find sources of information electronically. The design of individual volumes and chapters in this series takes this new access technology into account. SpringerProtocols makes it possible to download single protocols separately. In addition, Springer makes its print-on-demand technology available globally. A print copy can therefore be acquired quickly and for a competitive price anywhere in the world.

Saskatoon, SK, Canada ***Wolfgang Walz***

Preface

Topics of Research in General Anesthesia: State of the Art and Perspectives

The anesthetics used in everyday clinical practice are reassuringly safe. They provide us with a portfolio of rapidly acting and titratable agents. The technique used for the administration of anesthesia and monitoring of vital signs has also improved dramatically during these last decades. There is also a rapid development in surgery, surgical technique, and patients with complex and severe disease that are scheduled for surgery, along with a growing number of elderly and fragile patients having surgery. Thus, the demands for safe and effective anesthesia, securing not only a safe and effective intraoperative course but a rapid recovery following more complex surgery in the elderly and fragile patient, have become of outmost importance.

Stable intraoperative course with minimal deviation in vital signs, maintaining homeostasis with secure and adequate depth of anesthesia, avoiding any risk for unintentional light anesthesia, and subsequent risk for awareness with recall must be acknowledged. Avoiding too deep anesthesia and subsequent cardiovascular depression and prolonged recovery should likewise be avoided.

Goal-directed anesthesia, titrating anesthetics to each patients' unique needs, and balancing the surgical stress are common requests nowadays. Choosing an anesthetic agent may also impact quality of recovery and long-term outcomes. Combining drug choice and goal-directed drug delivery may indeed have an important impact on patient quality of recovery and potentially long-term prognosis. The potential risk for neurocognitive side effects during recovery has become a major concern in the handling of the elderly and fragile patients. Optimizing preoperative, prehabilitation, and fine-tuning anesthesia is important to understand in order to minimize the risk for postoperative cognitive side effects, postoperative delirium, and postoperative cognitive dysfunction. The effects on the cognitive function, both in the neonate and in the elderly, are a matter of debate. Extensive research is devoted to study the impact of anesthetics on the central nervous system, i.e., what can specific drugs impact and what impact do specific drugs have on the neuro-inflammatory response when associated to surgery and anesthesia. Further studies translating the basic research into the effect of surgery/anesthesia on the developing brain and in the elderly with signs and symptoms of dementia are urgently needed. Anesthetic techniques and their impacts on the prognosis in patients with cancer disease are also discussed. There are data suggesting that anesthetic choice may impact the risk for metastasis and cancer reoccurrence. There is also extensive research looking at the effects of anesthetics on cancer cells and systems involved in cancer progression. Preclinical research, as well as prospective randomized clinical trials, is ongoing.

We are currently at an exciting time where anesthesia has evolved from being tasked to only take care of patients during the surgical procedure to perioperative medicine specialty, supporting the patient throughout the preoperative preparation and postoperative period. Quality of recovery, avoidance of neurocognitive side effects and having long-term outcomes, and the development of chronic pain and disease progress are becoming the new objective for anesthesiologists.

Stockholm, Sweden *Jan G. Jakobsson*

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Chapter 1

The Challenge of Accidental Awareness During General Anesthesia

Marco Cascella

Abstract

Intraoperative unconsciousness and amnesia are main goals of general anesthesia. Although these objectives are achieved in the vast majority of cases, in very rare circumstances they are not "completely" obtained, or maintained, and in turn, accidental consciousness and subsequent memorization of sensorial information may occur during intended anesthesia. This failure of anesthesia is termed as *general anesthesia awareness* (or *accidental awareness during general anesthesia*, or simply *awareness*). While the incidence of this complication is rare, the clinical features and its potentially devastating psychological sequelae impose a thorough knowledge of the phenomenon.

During anesthesia, the patient may be occasionally cognizant responding to commands or may wake up. This intraoperative awakening, termed as "wakefulness," must be not confused with the awareness. The discriminating element for a proper definition of awareness, indeed, is the concomitant presence of two elements that correspond to higher cognitive functions: consciousness and memory processing of the intraoperative experience.

Although not all wakefulness episodes complete the memory processing (encoding, storing through consolidation, and retrieval), consolidated unexpected experiences can be expressed as explicit-spontaneous, or induced, reports. The pathways of this declarative, or explicit, memory produce, in turn, the *awareness with recall* phenomenon. Alternatively, the intraoperative experience can be processed without requiring conscious memory content and expressed as inexplicable changes in behaviors, or performances, or through the mechanism of priming, in which exposure to one stimulus influences a response to a subsequent stimulus, without conscious guidance, or intention. The processing of information via nondeclarative, or implicit, memory system, leads to the other awareness subtype: the *awareness without explicit recall*.

Referring to the state of the art of research, the aim of this chapter is to dissect the multiple aspects of this anesthesia-induced complication. Although in recent years research has allowed us to understand many aspects of the phenomenon, its complete characterization still seems far away, and several controversies and dark sides remain. In particular, the chapter addresses topics related to definitions and classification, epidemiology, clinical features, risk factors, management, and strategies useful for prevention.

Finally, the interest in the subject is justified as it represents a fascinating matter of investigation which intersects study areas in the contexts of the "general anesthesia research" and neuroscience. Mechanisms of anesthesia, and impact of anesthetics on consciousness and memory, represent an attractive way for studying brain and mind through an "experimental model" (general anesthesia) that is carried out on several tens of millions of patients, every year.

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Key words General anesthesia awareness, Accidental awareness during general anesthesia, Explicit memory, Anesthesia awareness with recall, Awareness without explicit recall, Memory consolidation, Memory processing, Benzodiazepines

Abbreviations

AAGA	Accidental awareness during general anesthesia
AAWR	Anesthesia awareness with recall
ASA	American Society of Anesthesiologists
AWER	Awareness without explicit recall
BDZs	Benzodiazepines
CIIA	Combination of intravenous and inhaled anesthesia
DoA	Depth of anesthesia
ETAC	End-tidal anesthetic concentration
GA	General anesthesia
GAA	General anesthesia awareness
GABAAR	Gamma-aminobutyric acid A receptor
IA	Intraoperative awakening
ICU	Intensive care unit
IFT	Isolated forearm technique
MAC	Minimal alveolar concentration
NAP5	Fifth National Audit Project from Great Britain
NMBAs	Neuromuscular blocking agents
NMDA	*N*-methyl-D-aspartate
NO	Nitrous oxide
PTSD	Posttraumatic stress disorder
TIVA	Total intravenous anesthesia

1 Introduction

Intraoperative unconsciousness and amnesia, respectively, the incapability of evaluating and processing the information of the environment and the abolished memorization of events that occurred while the patient is under the effect of anesthetics, are the main goals and the foundation of general anesthesia (GA). Although these objectives are achieved in the vast majority of cases, in very rare circumstances they are not "completely" maintained and, in turn, accidental consciousness and subsequent memorization may occur during intended anesthesia. This anesthesia complication, which has been referred to for many years as *awareness*, is generally termed as *general anesthesia awareness* (GAA) or *accidental awareness during general anesthesia* (AAGA). The awareness complication encompasses a spectrum of conditions with different clinical manifestations (Fig. 1).

Awareness during anesthesia is not a new problem because, interestingly, it was observed even at the beginning of the modern

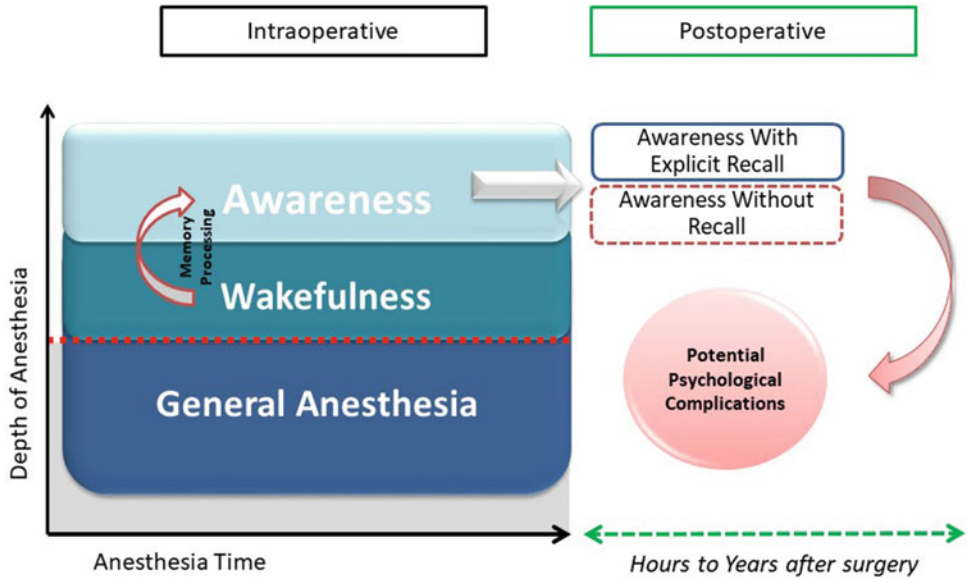

Fig. 1 General anesthesia awareness. Schematic picture and subtypes. During anesthesia, it is not always possible to maintain a state of deep anesthesia (below the red line). Again, patients may be occasionally cognizant responding to commands or may wake up. This intraoperative awakening is termed as "wakefulness." Although not all wakefulness episodes follow the pathways of memory processing (encoding, storing through consolidation, and retrieval), consolidated unexpected experiences can be expressed as explicit-spontaneous or induced report (declarative, or explicit memory), configuring the awareness with recall phenomenon. Alternatively, the intraoperative experience can be processed without requiring conscious memory content (nondeclarative or implicit memory) and expressed as inexplicable changes in behaviors or performances. Both awareness subtypes may be reported (awareness with recall) or expressed (awareness without recall) at the emergence from anesthesia but also at distance from the end of the intervention. Awareness may have psychological sequelae for the patient, including single symptoms (insomnia, depression, anxiety), or grouped into definite syndromes (e.g., post-traumatic stress disorder)

anesthesia. Morton himself described that his anesthetized patients were "half asleep" and experienced pain during the operation [1]. In 1950, Winterbottom described the first well-detailed clinical case in a correspondence to the British Medical Journal entitled "Insufficient anaesthesia". As the patient reported:

> *. . . I woke up in the theatre! ... I was awakened by the most excruciating pain in my tummy. I felt as if my whole inside was being pulled out. I wanted to cry out or otherwise indicate my suffering but I couldn't move any part of me. I heard the doctors talking about the gall-bladder and about doing something with it to the small intestine ...* [2].

Later on, in 1961, Meyer and Blacher [3] firstly illustrated the case of a patient that manifested psychological complications after an episode of awareness. This psychological manifestation was indicated as "traumatic neurosis" because the posttraumatic stress disorder (PTSD) had not yet been characterized by the American Psychiatric Association [4]. The authors titled the report "Traumatic Neurotic Reaction Induced by Succinylcholine Chloride"