Menizibeya Osain Welcome

Gastrointestinal Physiology

Development, Principles and Mechanisms of Regulation

Springer

Gastrointestinal Physiology

Menizibeya Osain Welcome

Gastrointestinal Physiology

Development, Principles and Mechanisms of Regulation

Springer

Menizibeya Osain Welcome
Department of Physiology, Faculty of Basic Medical Sciences
College of Health Sciences, Nile University of Nigeria
FCT-Abuja
Nigeria

The Figures in this book were designed with help of Motifolio Biomedical Drawing Toolkit Suite (Motifolio Inc., Ellicott City, USA).

ISBN 978-3-319-91055-0 ISBN 978-3-319-91056-7 (eBook)
https://doi.org/10.1007/978-3-319-91056-7

Library of Congress Control Number: 2018940411

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The digestive system is responsible for about 60–90% of diseases that affect humans, making the digestive system one of the most important systems in life processes. This book is a review of key findings of the last two and present millennia on the area of digestion. This text is a leading textbook and most comprehensive review ever written in the field of gastrointestinal (GI) physiology.

This book is written to address the gaps in other texts. This book provides key information, yet robust, required to have a detailed and contemporary understanding of GI physiology. This text incorporates key concepts of translational physiology by systematically examining pertinent areas of the GI system, including anatomy, embryology, histology, biochemistry, pharmacology, biophysics, behavioral science, bioinformatics, pathophysiology, public health, genetics, epigenetics, and therapeutics, in accordance with physiology. The text provides crucial information on the molecular, cellular, tissue, organ, and system levels of functioning of the GI tract in health and disease.

This book thoroughly explains the normal functioning of the digestive system in humans, relates the concepts to how diseases develop, and unravels the mechanisms and basis of medical approach to treatment of the different ailments of the GI tract.

This text apart from incorporating historical information on developmental course of GI physiology from antiquity to the contemporary era also outlines contemporary trends and gives a comprehensive description of developmental path that determined the study of digestive functions in the present-day world.

New data that have accumulated over the past decades on the functioning of the digestive system are systematically reviewed, and emphases are made on breakthrough studies. This book incorporates latest information on functional communication network between the gut and other organs and tissues of the body such as the brain, lungs, kidney, heart, pancreas, skin, bone, and adipose tissue. New information on the roles of the gut as endocrine, exocrine, and neural organ is not pretermitted. History of over 60 hormones and neurotransmitters currently discovered in the gut alone as well as their functional aspects are discussed. This book also provides detailed historical and functional information on all digestive enzymes. New information on mechanisms of enzymatic breakdown of food substances is also discussed. Recently discovered enzymes of the GI tract identified to play useful role in digestion are also reviewed.

The text strategically highlights key functions of the gut microbiota. Both traditional and emerging roles of *H. pylori* in gastric physiology are discussed.

This book is carefully designed for biomedical, medical, and health science students, scientists, and researchers. It also serves as an inevitable reference text for clinicians and other medical, health, and allied professionals.

For beneficial comprehension, the book is systematically divided into topics and subtopics. There are also numerous color illustrations. Recommended readings are separated into original articles, review articles, guidelines, books, and Nobel lectures.

The book contains special in-text references on some high-quality publications. Key information or exceptional discoveries of global significance are systematically outlined as "Spotlights." Concepts traditionally used in science, originating from historians or other areas of science other than physiology, are briefly described as "Reference Note." This is needed to provide an adequate and broader understanding of the information applied in physiology.

To aid comprehension of the association between the physiological concepts, principles, and clinical presentations, clinical examples such as pathologies that link basic science with clinical practice are outlined in special sections "Clinical Correlates." Contemporary approaches to the basis of treatment of some GI tract diseases are systematically outlined.

In addition to providing an adequate and broader understanding of the information applied in GI physiology, this approach addresses the challenges of translational physiology. It also provides the necessary background for application of basic science information to medical practice, as well as utilization of bedside clinical data and application to produce a solid knowledge base in physiology. This approach represents a high-quality evidence-based delivery of physiological information to the learner and allows the learner to appreciate the value and usefulness of physiology to nature and human existence.

Thus, the book applies the basic concepts of translational physiology. This design of the text is aimed at closing the gap between basic science and its application (such as in the clinics, public health), which is largely due to the reductionist approach, rather than an integrative in addressing human maladies.

Finally, I would like to take this opportunity to express my sincere gratitude to Prof. Vladimir Alexeevich Pereverzev MD, Ph.D., DSc, Head of Department of Normal Physiology of the Belarusian State Medical University, Minsk, Belarus, and the editorial team of Springer for all their support and encouragement.

FCT-Abuja, Nigeria Menizibeya Osain Welcome
March 2018

Key Features

- Most comprehensive, up-to-date text ever written in the field of gastrointestinal physiology in the world
- Basic and reference text for medical and allied health science students, as well as practicing doctors and other health professionals
- Provides a detailed analysis of the trend of development of knowledge on all aspects of gastrointestinal physiology from antiquity to the contemporary world
- Provides detailed mechanisms of regulation of gastrointestinal functioning in normal and pathology
- Outlines groundbreaking studies of the past centuries in the field of gastrointestinal physiology and provides contemporary information on the direction of future investigations
- Numerous color illustrations.

Target Groups

- Undergraduates and graduates of medicine, dentistry, pharmacy, nursing, human biology, science, and other allied health professions
- Interns, residents, and other practicing medical doctors as well as health professionals
- Academicians
- Researchers and scientists
- Policy makers.

Contents

About the Author

Dr. Menizibeya Osain Welcome, MD, Ph.D. is a Senior Lecturer in the Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Nile University of Nigeria, FCT-Abuja. He earned the Doctor of Medicine in 2011 and his Ph.D. in Medicine (Physiology) in 2013. He is the author or co-author of over 200 papers and holds several awards.

Chapter 1
History of Development of Gastrointestinal Physiology: From Antiquity to Modern Period and the Birth of Modern Digestive Physiology

Abstract Curiosity and the quest for addressing human maladies or problems of nature are possibly the key driving forces for discoveries in science. Apart from shaping the reputation of the scientists and historically inscribing his or her name in the memorable plate, outstanding discoveries in science gain varying levels of recognition from the local to the global stage. The Nobel Prize is the most respected honor and highest level of recognition given to any individual on planet Earth for exceptional contribution to solving key problems of nature and mankind. Since 1901, this highest accolade started recognizing extraordinary endeavor of scientists in addressing glaring issues of existence and nature. Traditionally, the prize is given in literature, physics, chemistry, and physiology or medicine. Over the past years, award recipients, probably due to the interchangeability and relationship between disciplines in science, scientists who are physicians and researchers in physiology or medicine, for example, have been awarded the prize not only in physiology or medicine, but also in chemistry. Chemistry and physiology or medicine have had a close relationship as regards discoveries that have necessitated the award of the Nobel Prize. Except in rare cases where the prize was awarded to a discovery that happened by chance, most awards were made to discoveries that had solid roots in the previous works of other scientists. Therefore, it is imperative to have a basic knowledge of the historic timeline of major developmental events and achievements to allow for meaningful future investigations that could fetch the world results for the betterment of life. Since its inception, out of 211 Nobel laureates in Physiology or Medicine, awarded between 1901 and 2016 (107 times of Nobel Prize awards), five laureates have received the prestigious award in the area of the gastrointestinal physiology. All five prizes were won by scientists whose works were rooted in previous works of other scientists. The research works of the scientists whose ideas laid the basis for breakthrough studies are worth considering. The first Nobel laureate in the area of gastrointestinal (GI) physiology, Ivan Petrovich Pavlov (1849–1936), who set the stage for breakthrough discoveries in GI physiology, is a physician, physiologist, and pharmacologist. He won the prize in 1904, making him the fourth scientist in the list of Nobel Prize Winners since the inception of the award in 1901. Apart from the Nobel Prize, there are other scientific prizes with

M. O. Welcome, *Gastrointestinal Physiology*,
https://doi.org/10.1007/978-3-319-91056-7_1

near equivalent rating to the Nobel Prize. Some of the scientific prizes are awarded specifically to young scientists. This chapter provides contemporary information on the historical timeline of events that transpired on GI physiology beginning from antiquity to the contemporary period.

Keywords Developmental history · Evolution · Nobel Prize · Antiquity Renaissance · Modern era · Modern digestive physiology · Gastrointestinal physiology · Gastric fistula · Digestion · Sham feeding · Pepsis Nervism · Heidenhain pouch · Pavlov's pouch · Translational physiology Translational medicine · Translational research · Reductionist · Integrative Physiome project · Giome Project · Hippocrates · Aristotle · Plato Herophilus (Herofilos) of Alexandria · Praxagoras · Andreas Vesalius Erasistratos of Keos · Susruta (Sushruta) Samhita and Charaka Samhita Claudius Galen of Pergamum · Magnus of Nisibis (or Emesa) · Alexandrias Byzantine physicians · Caelius Aurelianus · Soranus of Ephesus Avicenna · Norman Guitmund · Theodoric Borgognoni · Guido Lanfranchi (Lanfranc of Milan) · Johannes Guttenberg · Alessandro Benedetti Jacopo Berengario da Carpi · Leonardo da Vinci · Paracelsus · Johan Thölde René Descartes · Giovanni Alphonso Alexander Mikhailovich Ugolev Arne Dahlqvist · Borelli · Herman Boerhaave · Regnier de Graaf Friedrich Tiedemann · Leopold Gmelin · Jöns Jakob Berzelius Andrés Laguna de Segovia · Christopher Columbus · Jan Baptiste van Helmont Andreas Vesalius · Franciscus de la Boë Sylvius · Viridet · William Harvey Caspar Bauhin · Johann Georg Wirsung · Francis Glisson · Johann Conrad Peyer Johann Conrad Brunner · Johann Nathanael Lieberkühn · René de Réaumur Edward Stevens · Johann Nepomuk Eberle · Erhard Friedrich Leuchs Anselme Payen · Jean-François Persoz · Wilhelm Friedrich Kühne Andreas Sigismund Marggraf · Jean Baptiste André Dumas · Louis-Nicolas Vauquelin · Pierre Jean Robiquet · William Hyde Wollaston · Karl Axel Hampus Mörner · Jons Jakob Berzelius · Gerardus Johannes Mulder · Gabriel G. Valentina Apollinaire Bouchardat · Claude Marie Sandras · Louis Mialhe Albrecht von Haller · Fredericus Bernardus Albinus · Bernhard Siegfried Albinus Hermann Boerhaave · Albinus · Andreas Bonn · Abbe Lazzaro Spallanzani John Richardson Young · Guillaume Dupuytren · William Prout Camillo Golgi · Theodor Schwann · Johannes Peter Müller · John Newport Langley · John Sydney Edkins · John Howard Northrop · Roger Moss Herriott François Magendie · Sir Charles Bell · Theodor Schwann · Karl (Carl) Ludwig Ernst von Brücke · William Bayliss · Nikolai Konstantinovich Kulchitsky Karl Hugo Kronecker · Samuel James Meltzer · Saturnin Arloing Ivan Mikhailovich Sechenov · Edwin Burket Twitmyer · Sir Charles Scott Sherrington · Edgar Adrian · Johanes Andreas Fibiger · Henry Hallet Dale George Palade · James Whyte Black · Robin Warren · Barry Marshall Basov Vasiliy Alexandrovich · Sergey Petrovich Botkin · André Latarjet Lester Reynold Dragstedt · William Beaumont · Claude Bernard Jan Evangelista Purkyně · Rudolph Heidenhain · Ivan Petrovich Pavlov

Abbreviations

AD	Anno Domini
BC	Before Christ
BCE	Before Common Era
ca (syn. c., c, cir., circ., cca.)	Circa
CE	Common Era
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
HCl	Hydrochloric acid
mRNA	Messenger ribonucleic acid
NASA	National Aeronautics and Space Administration
α	Alpha
β	Beta
γ	Gamma

1.1 Introduction

Before elaborating the history of the development of gastrointestinal (GI) physiology, it is imperative to explain the meaning of physiology briefly and mention the characters that made substantial contributions to the development of the subject. Physiology is a word formed from the Greek words “physis” meaning nature and “logos” meaning study. Therefore, physiology can be defined as the study of nature and the essence of life processes. In a broader view, physiology means the study of life processes and functions and their dynamics at the molecular, cellular, tissue, organ, system, and organismal levels. It is the science of the life of an organism as a whole, its interactions with the environment, and the dynamics of life processes. Physiology can be delineated further as the science of life functions, its structures, and mechanisms of their realization and the principles of regulations [1].

The word “physiology” was first used by the Greek philosophers around sixth century BC to mean the inquiry into the nature of things. This view of physiology continued for several centuries. However, during and after the end of the Renaissance, the use of “physiology” included functions of human organs and systems (see below). There were different schools of thought on the subject of physiology across centuries. But the philosophical root and reasoning enmeshed in physiology and as defined by the ancient Greek philosophers was unavoidably transferred across generations until the nineteenth–twentieth centuries. According to the German physician, physiologist, and philosopher, professor Wilhelm Maximilian Wundt (1832–1920), “physiology is concerned with all the phenomena of life that present themselves to humans in sense of perception as bodily processes, and accordingly form part of that total environment which we name the external world." The increase in the quest for knowledge and curiosity of humans substantially enhanced the development of physiology in later centuries. This is unarguably true; however, the philosophical view of physiology was subject to unending discussion in the scientific community [1].

It is important to bear in mind that physiology is older than man is. It is man's inquiry into nature that has continued to unravel the principles and mechanisms of body functioning. Key personalities that made exceptional contributions to the fundamental development of physiology as a scientific discipline include Hippocrates (460–377 BC) who, among other things, observed that differences in the composition and movement of liquid of the body are the result of different psychological makeup of humans. Others include René Descartes (1596–1650), William Harvey (1578–1657), Daniel Bernoulli 1700–1782), Antoine-Laurent de Lavoisier (1743–1794), Mikhail Vasilyevich Lomonosov (1711–1765), Claude Bernard (1813–1878), Rudolph Heidenhain (1834–1897), Emil du Bois-Reymond (1818–1896), Karl Landsteiner (1868–1943), Santiago Ramón y Cajal (1852–1934), Camillo Golgi (1843–1926), Ivan Mikhailovich Sechenov (1829–1905), Alexei Alexeevich Ukhtomsky (1875–1942), Ilya Ilyich Mechnikov (1845–1916), Verigo Bronislav Fortunatovich (1860–1925), Schack August Steenberg Krogh (1874–1949), Carl Friedrich Wilhelm Ludwig (1816–1895), Christian Harald Lauritz Peter Emil Bohr (1855–1911), John Scott Haldane (1860–1936), Nikolai Evgenevich Vvedensky (1852–1922), Ivan Petrovich Pavlov (1849–1936), Pyotr Kuzmich Anokhin (1898–1974), Walter Bradford Cannon (1871–1945), David E. Goldman (1910–1998), Alan Lloyd Hodgkin (1914–1998), Andrew Fielding Huxley (1917–2012), Bernard Katz (1911–2003), Johannes Peter Müller (1801–1858), Justus Freiherr von Liebig (1803–1873), Carl Friedrich Wilhelm Ludwig (1816–1895), Sir Michael Foster (1836–1907), François Magendie (1783–1855), Silas Weir Mitchell (1829–1914), Henry Pickering Bowditch (1840–1911), Eduard Friedrich Wilhelm Pflüger (1829–1910), Sámuel Rácz (1744–1807), Elias Cyon (1843–1912), Henry Newell Martin (1848–1896), Oscar Langendorff (1853–1908), Frederick Gowland Hopkins (1861–1947), Walter Clement Alvarez (1884–1978), Curt Paul Richter (1894–1988), Alexander Mikhailovich Ugolev (1926–1991), and Arne Dahlqvist (1909–1995) [2, 3]. A couple of other scientists have contributed significantly to physiology; some of these scientists can be found on the Web site of the Nobel Prize (www.nobelprize.org), American Physiological Society (www.the-aps.org), International Union of Physiological Sciences (http://iups.org), and Physiological Society (http://www.physoc.org).

As a tradition, the study of physiology has been carried out at the molecular, cellular, tissue, organ, and system levels, and hence, physiology is divided into different subdisciplines: molecular physiology, cellular physiology, organ physiology (e.g., liver, lungs, or stomach physiology), system physiology (physiology of the nervous system or neurophysiology, physiology of digestive system or gastrointestinal physiology, physiology of the circulatory system or cardiovascular physiology, physiology of the respiratory system or respiratory physiology, physiology of the urinary system, and so on). Other areas of physiology that are taught as courses in higher institution include developmental physiology, geriatric physiology, physiology of labor, aviation and cosmologic physiology, ecological or environmental physiology, evolutional and comparative physiology. Also, to distinguish differences in functioning of different living things, physiology is classified as human physiology, animal physiology, plant physiology, fungal physiology, and microbial (viral, bacterial) physiology. The study of physiology combines information from other disciplines, including histology, embryology, anatomy, biochemistry, molecular and cellular biology, pharmacology, internal medicine, therapeutics. The study of the mechanisms of occurrence, course, and outcome of pathological processes and diseases is called pathological physiology (pathophysiology). Both physiology and pathological physiology are core disciplines in medicine and clinical practice, providing firsthand information on ways in addressing pathological conditions in the contemporary world.

This book deals specifically with "GI physiology." In this book, physiology of digestion and GI physiology are used interchangeably. Digestion is the process involving the initiation of secretions in preparation for the mechanochemical breakdown of food substances, intake of food, proper biomechanical breakdown from polymers to monomers with varying intensity at different levels of the digestive tract as well as the de novo formation of certain biomolecules in the colon and the absorption and transport of final products of mechanochemical breakdown or synthesis into the body fluids that subsequently serve for plastic and energy functions, and the removal of undigested products from the anus. The discipline that is concerned with this area of science is called GI physiology. It should be emphasized, however, that though the definition of digestion given above is far encompassing, it is not exactly complete, which we will see in later part of this book. This is because accumulating evidences indicate that not only monomers are absorbed in the intestine but also dimers or oligomers of not only peptides but also saccharides.

The hollow structure through which digestion occurs is the digestive tract (or alimentary canal). It is made up of mouth, pharynx, esophagus, stomach, small and large intestine, and the anus (Fig. 1.1). The GI system comprises of the digestive tract and accessory organs such as teeth, tongue, salivary glands, pancreas, liver, and gallbladder (Fig. 1.1). Digestion is regulated by a complex network of neural, hormonal, auto-para-juxa-crine, and electromechanical systems/factors.

1.2 Organization of the GI System, Periods of Development of Knowledge on the Digestive Physiology

Organization of the GI system is the arrangement of the constituent parts of the digestive system that ensure execution of its functions.

The first level of organization of the digestive system is called the chemical level. In this level, the system is viewed as being composed of molecules which are formed from atoms. In the second level, several molecules come together to form the cell, which is the smallest structural and functional basis of living things.

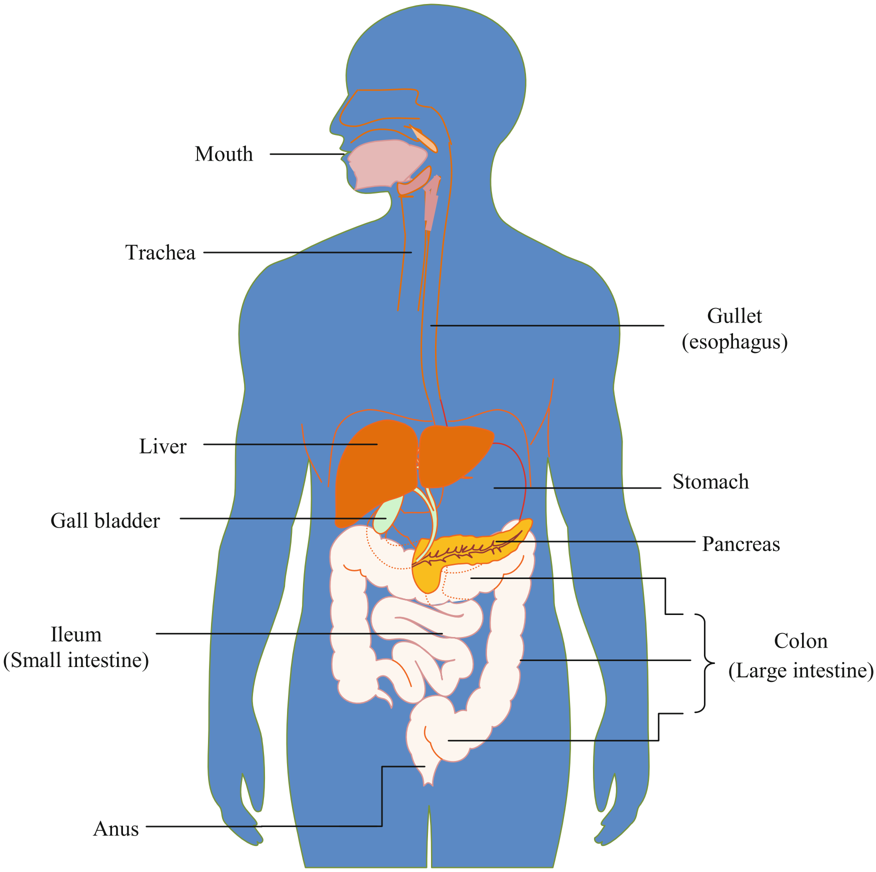

Fig. 1.1 Human digestive system. The digestive system comprises the digestive or GI tract and accessory organs. The tract starts from the mouth and extends from the pharynx down to the esophagus, and then to the stomach (a hollow muscular organ), which leads to the intestine (small and large intestine) and finally to the anus, the exit point of undigested products. The accessory organs of digestion are teeth, tongue, salivary glands, liver, gallbladder, and pancreas. Note that some of the terminologies/words used today in GI physiology and many other areas were formed from Latin and Greek words. For instance, the rectum was formed from the Latin "rectum intestinum," meaning straight intestine. The origin of other words used in GI physiology is discussed in the text

A group of similar cells forms tissue. A group of tissues forms an organ. An organ such as the intestine is formed from epithelial, neural, smooth muscle, and connective tissues. Different organs work closely together to form organ system level of organization. For instance, the GI system is composed of digestive tract (which itself contains organs) and the accessory organs. The organismal level of organization is comprised of many organ systems. The rise of knowledge in different areas of GI physiology may not be separated with precision since one period overlapped with other periods (Fig. 1.2).

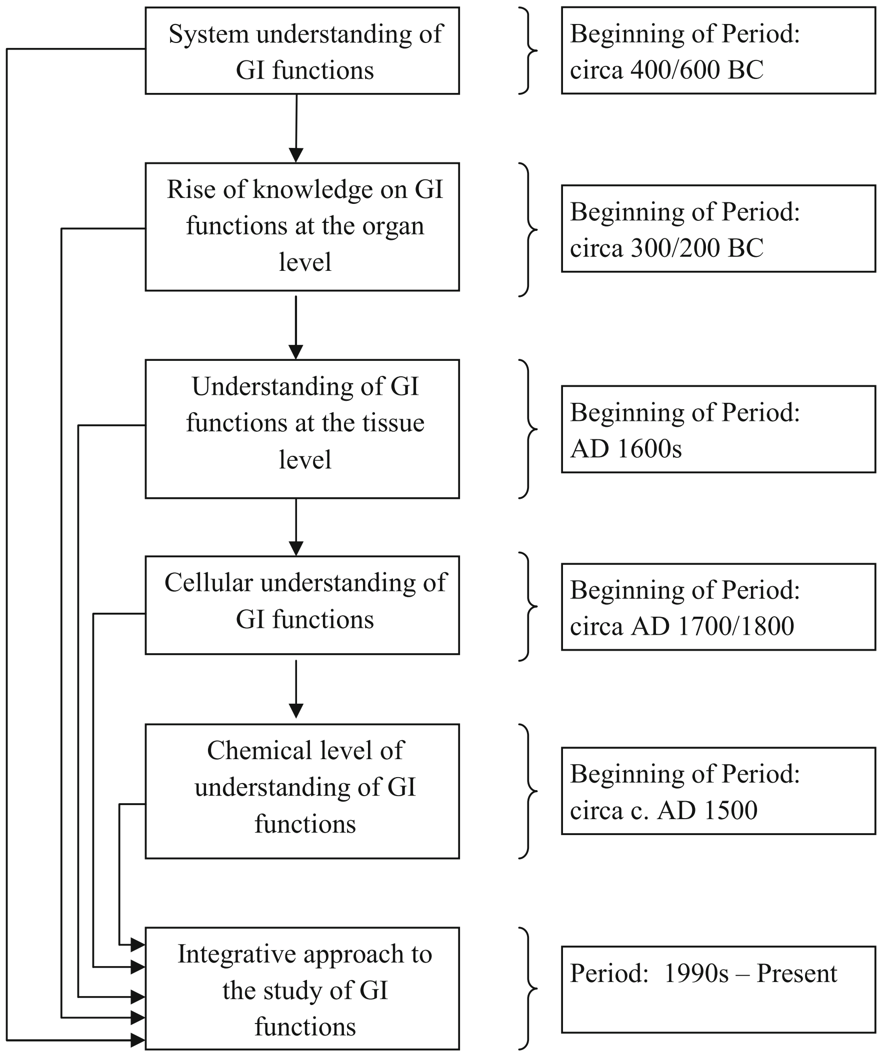

Fig. 1.2 Periods of development of knowledge on different levels of organization of GI physiology. Physiology evolved from initial understanding of the system functioning. This system understanding expanded subsequently to the study of separate organs, which also expanded to tissue and cellular level investigations. Chemical quest for the nature of physiological systems developed at a relatively fast rate and occurred almost simultaneously with cellular and molecular levels of development. All these levels of development, however, are interlaced, and no strong demarcation by time actually exists. The timeline provided in this chart is estimation. It should be pointed that the present trend in development of physiology is directed toward integrative approach, though relatively small research group investigators still study physiological systems at the cellular, molecular, and chemical levels

1.3 Evolutionary Emergence of the Gastrointestinal System

Digestion as a central role of the GI system was predetermined evolutionally, and this physiological process is executed according to the laws of nature. Because it serves other systems of the body, it could have been the first system to evolve and acquire higher specialization during the course of evolution. Digestion is a function present in all members of the animal kingdom ranging from single-cell organisms (with single body cavity) to mammals (with more sophisticated body cavity or tube). The emergence of the GI system is an important evolutionary feat that was required to support the future complexity of members of the animal kingdom. Importantly, complexity of the GI system increases with increase in complexity across phyla of the animal kingdom. The striking key functional similarities despite the diverse structural differences in GI system across different classes of the animal kingdom remain a crucial evidence of the emergence of the GI system during the Cambrian explosion, a period of heightened diversification of animals that may have been triggered or accelerated by environmental or biological factors. The striking similarities in functions despite diverse structural differences in GI system across different phyla of the animal kingdom not only are a testament, but also an important evidence of the emergence of the GI system during the Cambrian period. This suggests that the ancestral descendants of the primitive GI system sequentially rather than inorderly evolved, possibly, during the Cambrian explosion [4]. The Cambrian explosion is believed to have occurred around 542 million years ago in the Cambrian Period of the Paleozoic era. This event is estimated to have lasted for about 20 million years. Before the Cambrian explosion, majority of the organisms were single-celled or composed of colonies. Following this explosion, there was a significant acceleration of diversification of animal species, and over the next millions of years, the environment and its inhabitants gradually began to resemble that of today. Thus, the Cambrian explosion was responsible for the development of a true gut in the animal kingdom [5–8].

The pattern of emergence of the GI system's structure determined its functioning. The digestive process of single-cell organism is intracellular. However, the digestive process of simple multicellular organism is both intracellular and extracellular; thus, food is digested outside the cells in a digestive cavity or tract and then absorbed into the body. The emergence of both intracellular and extracellular digestion in multicellular organisms indicates an adaptive measure acquired during the course of evolution, which was required for enhanced provision of energy and survival. Recent investigations show similarities in digestive system of earliest animals, indicating that GI evolved from the simplest to more complex structure [4].

Across the phyla of the animal kingdom, there is a marked increase in complexity. A tube-like or sack-like structure was the first digestive apparatus to evolve in the animal kingdom comprising of nematodes (roundworms), annelids (earthworms), mollusks, arthropods (insects, crustaceans, arachnids, myriapods), echinoderms, and vertebrates (class fish, amphibians, reptiles, birds, mammals). But the simplest form of the digestive tube first evolved in the nematodes. The first digestive tubes in these animals may have occurred about 3.5–4 billion years ago. Nematodes were the first animals to have a true extracellular digestion; they have the most primitive digestive tract lined with epithelial cells. The tract starts from the mouth and extends through the pharynx down to intestine and to the anus. Food is taken in from the mouth and passes out from the anus. There is a marked gradual increase in complexity of the tube-like structure of digestion across the animal kingdom. There is also gradual increase in regional specialization of digestive functions and processes: chemical and mechanical digestion. Thus, the increase in complexity of digestive tract continuously increased with the evolution of a storage organ coupled with mechanical breakdown of food particles with enzymatic breakdown that previously evolved in plants and microorganisms (bacteria) [4–8].

The functional diversity of body processes coupled with increased search for foods that could compensate the increase in complexity of functions of multicellular organisms may have led to increase in complexity of GI tract in mammals. Unicellular organisms that inhabit higher organisms such as Homo sapiens are a testament to the evolutionary sophistication of digestion. The symbiotic relationship on which humans cannot live without certain population of microorganisms is a key surviving strategy that associates the simplest form of digestion with the most complex ones. Therefore, it may be deduced that different processes in digestion in mammals evolved in different stages in evolution and progressively increase in functional and structural complexity across the animal kingdom [4–8].

1.4 Digestive Physiology in Antiquity

The history of digestive physiology is related to human history as advancement in both knowledge and technology significantly and positively affected the development of physiology as a whole. In GI physiology, in particular, different mystical and philosophical views about digestion spanned across centuries before scientists could have a precise knowledge of the subject. The views and conceptions were mixed with misconceptions and philosophical reasoning. It should be mentioned that progress in digestive physiology was in part stimulated by the human strive to alleviate the sufferings of their fellows. Since antiquity, symptoms of GI disorders such as heartburn, belching, and epigastric pains were observed, and recommendations were made on feeding to ease these symptoms. This indicated that people at the time realized that effective digestion (via feeding with special "good" foods) was necessary to ensure adequate life processes of humans, though, at the time, no such word as "digestion" was known [9].

Digestion as a process had been in existence before humans became inquisitive on why food intake was necessary, the course of the swallowed food, and why feces were passed out. The ancient men wondered why the feeling to pass out feces following some hours of food intake was beyond the volition of man. It is necessary to emphasize, however, that before man's existence, other species had a functional digestive system. However, how they learned to gather food for energy and plastic functions could not be exactly ascertained. In the same line of view, human digestion may not have a precise origin due to the issues of human cognition and record keeping. Thus, history of digestion might not accurately define the timeline of events of human knowledge on the subject. Notwithstanding basic facts on digestion and the trend of development could be deduced based on available data and knowledge.

After humans had come into existence, they were at one time or the other hungry and became weak as they could not move easily from place to place and unable to carry out their daily activities, so they needed to satisfy their urge for movement and other activities. Hence, they tried to consume herbs and other substances. The initial results were, probably, both negative and positive as some herbs or substances could have led to constipation, diarrhea, and even death. Thanks to the physiological senses that would have helped man in distinguishing between bad and good food or substances, after experimenting with different food types and substances over a period. The experimental use of some of the herbs and substances obviously provided man with the required energy to move from place to place and carry out basic activities of life. These events probably led to man thinking that some spiritual forces were involved in food digestion [(they never knew that any bodily function or process like digestion existed, even though they were aware that food must be taken into the mouth (if necessary chewed), swallowed to feel strong and faces passed out after a given period of food intake)] [10]. Almost in every culture and society, the result of consumption of food was tied to one form of spirituality since in some cases consumption of certain food led to sick people regaining health and strength, people who were apparently not sick suddenly developing sickness or even dying subsequently. At one time, the Egyptian papyruses were thought to have suffered from spiritual forces when they developed diseases related to digestion. Though highly learned men as at the time made suggestions on the physiology of digestion, the course of ingested food remained a mystery that further fueled the concept of spiritism. In ancient Greece, Rome, Chinese, and India, philosophers and scientists made numerous proposals on digestion myth and how it occurred in humans.

Reference Note 1.1

Meaning of the Historical Designations—AD, BC, CE, BCE

Confusion usually arises when historical dates are used in research or academic texts. Religious historians were probably the first to have proposed various systems of identifying dates. The widely recognized ones are the "AD, BC, CE, and BCE." The abbreviation "AD"—Anno Domini, meaning "in the year of our Lord" or Anno Domini Nostri Iesu (Jesu) Christi, meaning "in the Year of Our Lord Jesus Christ," is a little over two millennia ago; "BC"—Before Christ; "CE"—Common Era; "BCE"—Before Common Era. The historical designation system "AD/BC" is similar to "BCE/CE" (i.e., AD is equivalent to BCE and BC is equivalent to CE). Therefore, 210 CE is the same as AD 210. These designations were used since the middle period. Remember that there is no zero year in these systems. The AD/BC system is based on the Julian and Gregorian calendars. The Latin abbreviation "AD" is placed before the year number, while "BC" is put after the year number (e.g., AD 2000, 210 BC). The numbers can be used as century or millennium. For example, nineteenth century AD is the same as second millennium AD. The BCE/CE system was developed not only by religious heads but also by scientists. Some scientists designated the period after the Year of Our Lord as "Vulgar Era" and became increasingly popularly used. During that time "Vulgar" means "common." The date of birth and death or reign of an individual may have different historical dates due to inadequate record keeping and different views and research data acquired by various historians. Notice that Galen's year of death is represented with two separate years (216/210). This is because the period represented is not exact, as with many other historical dates. To avoid the cumbersomeness of two separate dates, only one date may be represented using the "circa" attached. Circa is a Latin word meaning "about," i.e., approximately, and usually refers to a date. It is used when the date of an event of somebody is not exactly known. The word is used before the date that is not precisely known. Circa may be used in full or abbreviated as ca, ca., c., c, cir., circ., cca. Thus, Galen's existence on Earth could be written as 129–c. 210.

The Helenians theorized that food when taken is changed in the stomach to chyme and then to basic systemic fluids—blood, mucous, lymph, and bile [10, 11]. The father of medicine, Hippocrates (460–377 BC) who is reported to have introduced the term "pepsis" to mean digestion, may have advanced the view on digestion that set the stage for initial scientific exploits. He performed series of experiments on different parts of the organism, including the esophagus [12]. Other philosophers and scientists that lived during the period also made significant contributions to the subject of digestion. The Greek philosopher and scientist, Aristotle (384–322 BCE), born in the Macedonian city of Stagirus, contributed substantially to the understanding of digestion. He wrote several books on science to mark his contributions: History of Animals, Parts of Animals, Generation of Animals, Motion of Animals, Progression of Animals, Parva Naturalia, and De Anima [13, 14]. The numerous works produced by Aristotle generally on the life of the animal (and man) indicated that he was a fountain of knowledge. Aristotle made mention of an organ that connected with breathing, referring to the gullet and stomach, and suggested that they were necessary for food digestion. Unfortunately, at one time, he rejected the role of the stomach wall in digestion. Aristotle's vast knowledge in science is no surprise as his father Nicomachus was a physician, who worked with King Amyntas of Macedon. Thus, Aristotle must have learned and heard from his father speak about digestion. In addition, the fact that Aristotle studied under his mentor, Plato (ca. 428–347 BCE), a classical Greek philosopher and mathematician, could suggest that Aristotle must have been taught some basic concepts of life, a lesson that might have involved digestion. Similarly, Plato, who was a student of Socrates (ca. 470–399 BC), a classical Greek philosopher, could have listened to lessons on life from his mentor. He rightly identified the location of the liver and the approximate topography of the intestines. Although different philosophers and scientists had their views on science and life generally at the time, some of the concepts raised by Aristotle, Socrates, and Plato must have set the stage for other philosophers and scientists for the initial development of physiology of digestion. Unfortunately, many of their views were also tied to spiritism and entangled with misconceptions [2, 3, 13].

In the early days of the reign of science and philosophy, in antiquity, the Greeks continued to actively investigate the digestive system and terminologies were been identified for specific parts of the GI tract by the pioneer Greek philosophers. Herophilus (Herofilos) of Alexandria (ca. 335–255 BC) described the salivary glands (organs located around the mouth mostly involved in secretion of fluid of varying composition for the purpose of effective digestion) and named the first part of the small intestine following the stomach, duodenum because its length was 12 Greek measures. Herofilos was actually born in the Greek town of Chalcedon, Asia Minor, and schooled under the guidance of Praxagoras, a renowned anatomist and physician who taught at the Hippocratean medical school on the island of Cos (Kos). After completing his education, Herophilus moved to the city of Alexandria to practice medicine, during the reign of the first two Ptolemaic Pharaohs [15, 16]. Following his return to Alexandria, surprisingly, Herophilus abandoned the principles of his teacher Praxagoras. He rightly rejected cardio-centrism and followed the Hippocratic teachings on the soul and body when he proposed that primary parts of the human body are perceptible by the senses. Obviously, he was a proponent of the Hippocratic encephalo-centrism [17]. It was in Alexandria that Herofilos became well acclaimed for his discoveries. It was Herofilos who became the first to accurately describe the liver and its structure (The liver is a large gland located in the upper right quadrant of the abdomen, just beneath the diaphragm, and takes part in digestive and non-digestive functions). He was also the first philosopher and scientist to have investigated the pancreas, a glandular organ of digestion having endocrine functions. Herofilos might have been positively influenced by the city he lived. The city of Alexandria, Egypt, at the time of Herofilos, had the largest book repository in the world. Being one of the great physicians of Antiquity and regarded as the father of anatomy, Herofilos made phenomenal discoveries not only in anatomy, but also in physiology. His close rival in terms of intellectual capabilities may be Andreas Vesalius (1514–ca. 1564) who is regarded as the founder of modern human anatomy (see contributions of Vesalius below) [15, 16].

Another Greek philosopher and scientist who reigned during the time of Herofilos, Erasistratos of Keos (ca. 310–250 BC), proposed that after food intake, some processes occur in vivo because of the sounds of peristalsis during active digestion of food substances. Besides, he noted that food substances pass into the blood, and they could get to other parts of the body. This genius suggestion by Erasistratos may have been the first on food absorption in the GI tract [2, 18].

The ancient Chinese tied their belief to the tastes of herbs, which indicated the value man placed on food quality and digestion of food. However, food, and if at all they knew anything about digestion, it was associated with religion and spirituality as was inherent in other cultures. However, during the Zhou dynasty (ca. 1000–256 BC), the value of physiological regulation of digestion (and physiological systems in general) must have increasingly received recognition. As part of that physiological regulation, which was, though, still widely believed to be a misery would have been how food was eaten and how it transformed, whether to the body fluid or it formed waste or spirits. During the time, organs of digestion were known, for instance, the liver; however, the Chinese philosophers of Antiquity believed that these organs were present in humans on mystical reasons. Rather than the liver being the organ necessary for digestion, they asserted the process of digestion to the functions of the spleen. In addition to the stomach, other organs such as the gallbladder, intestines, and urinary bladder were all considered to be involved in digestion. Importantly, it was believed that digestion was necessary for providing nutrients to the body and delivering waste products out of the body. Interestingly, ancient Chinese associated good nutrition to healthy living as they warned against overeating or drinking, and ingestion of spicy foods [19]. The Chinese were probably the first to have associated GI dysfunctions with excessive emotions. The Chinese believed that ingestion of herbs was necessary to treat different diseases related to digestion. Unfortunately, during the time, like in many cultures, the ancient Chinese had poor knowledge of anatomy and physiology of the digestive system, which led to the death of numerous people as some procedures that could have saved life were still considered taboo and dangerous to the existence of the spirits [19].

Widely acknowledged personalities in Indian physiology or medicine are Susruta (Sushruta) Samhita and Charaka Samhita. The Vedic philosophical teachings of these personalities formed the basis of the ayurvedic medicine (Indian traditional medicine), which is considered to be one of the oldest known systems of medicine in the world today. Globally acknowledged oldest texts in medicine were introduced by Susruta and Charaka. Susruta, a ca. 600 BC physician, provided important anatomical information in the sixth century BCE; however during this era, in their vicinity, more attention was given to anatomy, rather than regulation of physiological systems [20]. Nonetheless, Susruta advocated moderate exercise for ancient Indians because it increased digestion, suggesting that digestion, they acknowledged, was important for health [21]. Charaka, a physician and physiologist, relied heavily on physical examination and direct observation to address human maladies, indicating that Charaka had a relatively good background of body systems and their functioning. In fact, it was Charaka that introduced the concept of digestion and metabolism in India. He emphasized the importance of not only cleanliness, exercise, and lifestyle in disease treatment, but also a healthy diet, which indicates the value and above all the knowledge background of the people at the time on digestion [22].

A review of physiology of antiquity will not be complete if the name and contributions of one of the Great physiologists, Claudius Galen (AD 129–216/210) of Pergamum (now Bergama, Turkey), are not mentioned. This is particularly important because, besides, his contributions, the period of antiquity ends with the death of Galen in circa 210 CE. In addition, Galen's knowledge and school of thought formed the basis of the Galenical school of physiology and medicine, which was the leading academic and research institution at the time. Unfortunately, the death of Galen marked the end of Galenical school of physiology and medicine. This renowned Greco-Roman physician and physiologist pointed out that digestion started in the stomach from where food substances were passed into the intestines (bowel). Further, Galen proposed that in the bowel, these food substances are decomposed and are transported to the liver through blood. This view of digestion was obviously from a genius. As we now know today, Galen was very close to the truth even though there was no useful experimental tool at the time that could provide proof of his hypothesis. He later, however, wrongly attributed that some mythical forces (such as animal heat), based on the initial Hippocratic view, were involved as a driving force in digestion. Another false attribution to digestion made by Galen was that the content of food eaten determined the volume of blood. I suppose Galen would have proposed that food substances consumed increased the concentration or level of corresponding nutrients in the blood. Of course, it would have been difficult for anybody to propose, for instance, that carbohydrate food increased the blood level of sugar. Philosophers and scientists at the time knew nothing about food nutrient types (such as sugar, protein, lipids) and blood sugar have not been discovered at the time. However, Galen's proposals laid the background for productive studies into the process of digestion [10]. Galen also proposed that food digested to produce heat—referred to as Galen's thermal theory of digestion. Some teachings of Galen lasted for about 1300 years until the Renaissance [23].

1.5 Digestive Physiology During the Renaissance

The Renaissance period (Renaissance is a French word meaning new birth) was marked with changes in culture, politics, diplomacy, increased scientific experiments in Europe. The period spanned from the fourteenth to the seventeenth century. Scholars of history suggest that this period was a connecting period between the middle and modern periods. The modern history (period) started after the postclassical era (middle period or middle ages) and after Renaissance period. The period must have started during the sixteenth–seventeenth centuries. The modern period is sometimes divided into the early modern period and the late modern period after the French Revolution and the Industrial Revolution [24, 25].

The Renaissance period opened the way for everybody to learn, invent, and borne new ideas for societal benefits, as opposed to the middle period when only a few (especially religious heads and societal leaders) were privileged to learn. Although there is no agreed consensus on the specific name or duration of this period, it may represent the period that starts after the fall of Rome in 476.

Renaissance must have closed with the discovery of America by Columbus or other notable events that took place in various parts of the world, including after the fall of Constantinople around 1453 [24, 25].

Contrary to antiquity, some people during Renaissance thought that digestive system did not have innate spiritual forces since it was filled with impunity. The period was marked by outright rejection of some of the teachings of Galen. For instance, Galen's century-old humoral and thermal theories on the functioning of the human body were rejected by evolving scientists. In some cases, Galen's view on digestion was completely debunked and considered a thing not worthy of discussion among the religious people, whereas in other situations, anybody who challenged Galen's theory on digestion was worthy of facing a tribunal for punishment and possibly sentencing to death. Some of the heads of the religious faith did not believe in the new science that was emerging during the period. Norman Guitmund (c. 999–1095), Bishop of Aversa, a Benedictine monk who was an opponent of the teachings of Berengar of Tours and never accepted Galen's theory of digestion. Guitmund fervently argued that religious ceremony such as the Lord's Supper performed at the alter is not subject to the laws of bodily digestion with respect to normal bread and wine. He completely rejected the notion that the sacraments can corrupt or decay as he argued that Christ can never corrupt nor decay, for Christ is the food of eternal life [26]. Like other religious groups, the Muslims outrightly punished individuals who proclaimed ideas of authorities such as Galen. Thus among the people of faith, only those teachings of their spiritual leaders were allowed and anybody seen proclaiming self or the teachings of any philosopher or scientist not of their faith was considered an evildoer, liable for punishment or death. In addition, the series of wars that occurred in different parts of the globe also hindered scientific developments as many works were destroyed and scientists killed. So, history of digestive system would not be complete if these events that caught short the lives of scientists or that must have wasted valuable works are not mentioned.

Progress in science and technology generally was greatly hindered during AD 200–1500 because of different cultural and religious ideologies. In fact, many writings of scientists were destroyed or burnt, and the life of some was truncated. These scientists died because of heresy as their opinions were at variance with the official or orthodox teachings [27]. Both scientists and physicians suffered a lot from the religious sector and government. Some scientists were imprisoned, sent into exile, guillotined, banished, blinded, beaten, shot, burned, for opposing the teachings of top authorities [28]. The great anatomist and physician from Spain, Andreas Vesalius (1514–1564), who discovered pulmonary circulation of blood (also known as lesser circulation) together with other scientists were tortured, and some copies of their books burnt to dust and charcoal. Although saliva was widely known to be a secretion of the mouth, the secretions of stomach and intestines were only been speculated upon during the early days of scientific endeavors, which was probably due to the difficulties involved in researching the gastric content since technical knowledge at the time did not allow investigating gastric secretion in vivo. Subsequently, Andreas Vesalius (1514–1564) conducted one of the most notable dissections that exposed the human body structure; chyme was noted to be present in this dissection. In his book, *De Humani Corporis Fabrica*, published in Basel in 1543, which formed the basis of modern anatomical research and medicine, also had numerous details and was accurate conserving the encephalocentric teachings of Hippocrates. The chyme was thought to be formed from ingested food and gut secretion. However, he did not report on the secretions of other regions of the gut. Marcello Malpighi of Bologna (1628–1694), a globally acclaimed anatomist and leading pioneer in liver, kidney, and spleen research, was subjected to physical assault by his foes and people who strongly disbelieved his scientific findings. It should be noted, however, that scientist received tribulations even from their colleagues. For instance, Johann G. Wirsung (1600–1643), a Bavarian monk and physician, who discovered the excretory duct of the pancreas in 1642, was tortured and later killed by his university professors and fellow physicians [2, 28].

While Galenical school of physiology and medicine crumbled in certain parts of the world, some scientists even leading scientists continued to retain the school of thought of this most renowned Greco-Roman physiologist of antiquity. Surprisingly, however, a few scientists who rather than proclaiming, opposed the teachings of Galen, were punished and even killed [28]. Thus, the teachings of Galen, arguably, were considered to be sacred and received various levels of acceptance across the globe during the Renaissance.

The Italian physician and surgeon, Guido Lanfranchi (1252–1315), also known as Lanfranc of Milan (ca. 1250–1306), Archbishop of Canterbury and student of the Italian surgeon and cleric Guglielmo da Saliceto (also called Guilielmus de Saliceto, William of Saliceto or Guillaume de Salicet, ca. 1210–1277), was outspoken critic of Galen school of thought on the thermal theory of digestion. Lanfranc was among the first scientists that received torture due to differences in political ideologies. He escaped persecution in Italy and traveled to Paris to settle in 1295, where he earned respect as the best surgeon in the country at the time [2, 28].

In Asia, pro-Galenic and anti-Galenic scientists and philosophers formed two strong opposing groups across the continent. Anti-Galenist scholars were mostly the religious heads, whereas the pro-Galenists were more of the scientists and physicians. The well-acclaimed Persian physician Avicenna (980–1037) was in concordance with Galen's view on digestion. Avicenna was a leading scientist in Asia and became renowned throughout the world. He made numerous contributions generally in medicine [29–31].

The theory of digestion flourished in Alexandria (Egypt) during the fourth–fifth centuries. More importantly, a crucial link between digestion and extragut organ (precisely the kidney) functioning was documented for the first time. Alexandria, being a city of academicians that housed some of the biggest libraries in the world during the time, produced renowned scientists on kidney functions and diseases, who taught digestion and urinary physiology (and medicine in general). The ancient nephrologist, Magnus of Nisibis (or Emesa), who taught medicine in Alexandria, at one time, may have pointed the link between food intake and urination [32]. This link will later be called the gut–kidney axis, which is discussed in Chap. 15 of this book. As globally recognized as the city of knowledge at the time, where numerous learned men lived, Alexandria had numerous resources for intellectual excellence. During the reign of the Alexandrias, Byzantine physicians (fourth–twelfth centuries AD) also made some observations on digestion [33]. The Byzantines were mostly interested in craniomaxillofacial medicine and surgery; they studied the mouth, the first region where mechanical and chemical digestion took place. They also studied the salivary glands as an accessory organ of digestion [33].

As a noted trend in the development of knowledge, many findings in the subject of digestion were made by physicians and scientists at the time as they searched for the causes of digestive problems while trying to provide solutions to sick people. The physician, Caelius Aurelianus (ca. AD fifth century) of Sicca Veneria, Numidia (now in Algeria), wrote many volumes on "*De morbis acutis et chronicis*" ("Concerning acute and chronic diseases") [34]. However, his works are largely adapted from those of Soranus of Ephesus (ca. 98–138 AD), a lucid Greco-Roman physician and second-century leader of the Methodist school of medicine. Ephesus was an ancient city in Ionian (Greek) Asia Minor, now western Turkey [35]. Another intersystem functional relationship was thought to exist between digestion and mental consciousness (central nervous system) by the Greek scientist. Although epilepsy (a disease involving the central nervous system due to disorders in neural pathways characterized by seizures and loss of conscious) was noted by the Assyrians and Babylonians circa 2000 BC, Hippocrates became the first to dispute that the disease was a divine malady or demonic possession, and notably, Caelius Aurelianus and Soranus of Ephesus genius proposed that patients should be treated with remedies that help digestion, pointed to a possible link between digestive and brain functions, even though it was not completely known at the time that epilepsy was a disease of the brain [34].

Religious heads that had a vast knowledge of science used scientific experimentations to strengthen their spiritual teachings and doctrines, which made their followers not only to have a better understanding, but also believed in the teachings of their leaders. The Italian surgeon, Theodoric Borgognoni (1205–1296), who later became Bishop of Bitonto in 1262 and then Bishop of Cervia appears not only to have made contributions to blood circulation. He was reported to have made illustrations that included the structure of the digestive tract of humans. His physiological understanding of the human body and ability to provide illustrated answers helped his followers had better understanding of his teachings and doctrines [36].

The mode of communication and information dissemination significantly hampered the growth of science during this period as knowledge was spreading slowly during this time, and results of experimentation in one region did not usually get to the people in other regions of the world. However, with a gradual increase in the number of travelers and number of people interested in science, there was a marked improvement in understanding of the human bodily functioning. Unlike nowadays where information can get to anyone located in any part of the world in seconds or milliseconds, information was disseminated during the time especially through traders and people who sailed around the world to find out what was happening in other regions. Movable-type printing was only introduced in 1450 by the German, Johannes Guttenberg (1395–1468) [28], which significantly increase dissemination of information by the publication of numerous texts in arts, science, and medicine. The first medical book was printed in 1478 and contains the works of many renowned physicians and scientists. This exclusive discovery of printing in Germany would give an opportunity for the printing of the first physiology textbook in the world, which will also aid better understanding of the digestive system.

The period was also marked by freedom of expression and fast advancement of science, especially in Europe. Some acts that were previously considered a taboo could be executed on the premise of scientific exploits and advancement. The first public postmortem dissection of two human bodies in 1315 in Bologna, Italy, significantly improved hypothetical understanding of the human body, including the digestive system and related organs [28].

As philosophers and scientists became more aware of the structure of the digestive tract, numerous proposals were made on the functions of the tract and associated organs. Unfortunately, scientists in those days had a very little or no chance in studying the functions of digestive tract as technological progress could not allow for groundbreaking studies in science. However, the possibility of increased need for experimentation grew as proofs were required for the numerous hypotheses made on bodily functions. In 1497, Alessandro Benedetti (circa 1450–1512), an Italian anatomist and physician, thought that the digestive tract, described to comprise of the stomach and intestines, was impure and as a result did not have connection with the seat of mind. He placed huge importance to experimentation, rather than valuing the words of authorities such as Aristotle or Galen. At this time of history, precise knowledge on the structure of the digestive tract has not been formed. Obviously, scientists needed to first understand the structure of the digestive tract before achieving meaningful understanding on the functions of the tract. Further information on the structure of the digestive tract was provided by the Italian physician, Jacopo Berengario da Carpi (also known as Jacobus Berengarius Carpensis or Jacopo Barigazzi or Giacomo Berengario da Carpi) (1460–1530). During the fifteenth century, Jacopo Berengario da Carpi noted that the anus was linked to the intestines and the mouth was linked to the gullet [2, 37]. His suggestion provided one of the first precise anatomical overviews of the GI tract. Thus, by the description of da Carpus, the structure of the "gut" was near complete and now known as a tract that connects the mouth to the anus.

A well-pronounced personality at the time, Leonardo da Vinci (1452–1519), was an Italian polymath, painter, sculptor, architect, musician, mathematician, engineer, inventor, anatomist, geologist, botanist, and writer, who also contributed to the anatomical understanding of the GI tract. His numerous contributions to anatomy and the drawings that show different structures, organs, and systems also included the digestive system. Leonardo da Vinci suggested that the digestive system helped respiratory functions. This genius suggestion, as we now know is the gut–lungs axis, which is useful in respiration (and more importantly, the two organs functionally support each other). This unique relationship will be briefly discussed in later part of this book. Interestingly, da Vinci argued that digestion involved not only the organs but also the abdominal muscles because they contracted and relaxed. He was probably referring to the role of abdominal muscles in respiration. Unfortunately, he wrongly attributed it to the digestive system. It is possible that rather than mentioning the abdominal muscles, he meant to say stomach muscles, when he was talking about the role of the muscles in digestion [38–40].

The Renaissance period may have ended with the rise of new concepts of understanding of the digestive functions; notably, iatrochemical and iatromechanical views of digestion were borne during this period (ca. 1500). The German physician and alchemist, Paracelsus, born Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1541), was keen to observation and could trace that some diseases including GI-related malfunctions were related to psychological dysfunctions. As a pioneer of physiological chemistry, Paracelsus thought that the stomach was functioning as a chemical laboratory within the body. Thus, he tried to use alchemical theory to explain digestion. Paracelsus noted that the content of the stomach was acidic. But he incorrectly reasoned that the acidity of the stomach was due to drinking of acidic spare water, which he called "acetosum ensurinum," meaning "hungry acid." Paracelsus further mentioned that the stomach acid was catalytic in action, necessary to prevent the formation of precipitations. Paracelsus and the work of other alchemists laid the foundations for discovering the exact chemical nature of this hungry acid. Around the same period, the German Alchemist, Johann Thölde (1565–1614), was probably the first to identify the hungry acid as hydrochloric acid (HCl) [9]. The iatrochemists also found other types of fluid in the GI tract. The Dutch physician, anatomist, and physiologist, Regnier de Graaf (1641–1673), was a classical iatrochemist, who studied the chemistry of digestion and the action of pancreatic juice. In 1664, De Graaf suggested that the juice obtained from pancreas was alkaline in nature [41]. However, the nature of GI juice remained to be fairly understood. In 1826, the German physician, anatomist, and physiologist, Friedrich Tiedemann (1781–1861), and the German chemist, Leopold Gmelin (1788–1853), became the first scientists to demonstrate the alkalinity of pancreatic juice, which was necessary for adequate digestion in the intestine. At age 35 years, Tiedmann became a professor of physiology and anatomy. Gmelin, a German chemist professor, conducted research not only in chemistry, but also in physiology. He worked on the nature of gastric acid by conducting several in vitro experiments. Furthermore, Tiedemann and Gmelin showed that the mixing of pancreatic juice and bile enhanced digestion of proteins. In 1835, the Swedish Uppsala University-trained physician and chemist, Jöns Jakob Berzelius (1779–1848), introduced the concept of catalysis as a necessary process for the formation of biomolecules. For Tiedemann, Gmelin, and Berzilius, there was no place for a vital force or spirits in digestion [2, 42–44].

As opposed to the alchemists, the iatromathematicians (also called iatromechanists) made some contributions to the understanding of mechanical aspects of digestion. They reasoned that digestion is an act of trituration (i.e., reduction of substances to smaller pieces by mechanical grinding/mixing). Their principles of digestion and medicine as a whole were based on mechanics, as they paid little or no attention to the role of chemistry in physiology or medicine. Pioneer iatromathematicians were the French philosopher and scientist, René Descartes (Latin—

Renatus Cartesius) (1596–1650), the Italian physiologist, physicist, and mathematician, Giovanni Alphonso Borelli (1608–1679), and the Dutch physician and physiologist, Herman Boerhaave (1668–1738), as well as Andreas Vesalius (1514–1564). Vesalius notably described digestion as a mechanical process and debunked Paracelsus's suggestion that digestion was a chemical process. So, at this point, at least three types of digestion were recognized: chemical, mechanical, and mixed (mechanochemical) [45–49]. While the iatromechanists exclusively believed that bodily functions could be explained with mechanical concepts alone, another school of thought believed that bodily functions including digestion could be explained by both iatrochemical and mechanical theories and not one alone. These iatromechanochemists were the British scientists. These different schools of thought on digestion spanned from the sixteenth to the early decades of the eighteenth century [50].

At this point in history, the digestive system and the possible processes occurring in vivo during food ingestion were becoming clearer. It should be borne in mind that the numerous views on the digestive system did not change; however, fundamental concept or level of knowledge on digestion gradually improved over time. At a certain period, there was relatively huge spread of information on digestion and science and art in general. Although knowledge on digestion spreads during time of Christopher Columbus (1450–1506), particularly due to commerce, colonization, and exploration, the information was accompanied with misconceptions and mainly composed of philosophical reasoning or mythology [51].

1.6 Digestive Physiology in Modern History

Understanding of digestion in the modern history did not mean that humans had modern views of digestion. It only depicts the period of the history of human development. The start of modern era was accompanied with substantial development in physiology and science in general. The first part of the seventeenth century emerged with increasing emphasis on hypotheses and experimental data [10, 27]. This period is regarded by some authors as the beginning of modern physiology [10, 27]. During this period—the seventeenth century—a Flemish chemist, physiologist, physician, and follower of Paracelsus, Jan Baptiste Van Helmont (1580–1644), provided the first chemical explanation of digestion, representing a key transition from alchemy to experimental chemistry. He not only showed that digestive agent in the stomach was a specific type of an acid, as opposed to the hungry acid, but also proposed certain chemical agents in the stomach juice were necessary for digestion. According to one of his theories on fermentation, Van Helmont proposed that ferments were chemical substances responsible for digestion and all physiological processes in the body. However, as it was later known, many works of other scientists on physiological systems did not at all confirm the reductionist thinking of Van Helmont. Consequently, Van Helmont's theory was ignored at the time. However, accumulating research evidences in the contemporary world over the past decades have undoubtedly shown the presence of fermentation in intestines by resident microbiota—population of microbial commensals in the intestines that are capable of digesting food substances where the organism's enzymes cannot digest. Van Helmont is also credited for discoveries in other fields. He introduced the word "gas" and also identified carbon dioxide (gas silvestre), carbon monoxide, nitrous oxide, and methane. Given his contributions to physiology and particularly digestion, the theories of Baptiste Van Helmont must have marked the beginning of digestive physiology [52].

A proponent to the fermentation theory of digestion, Franciscus de la Boë Sylvius (1614–1672), a renowned professor of medicine in Paris and Leida (France), during the seventeenth century, agreed with postulator of the modern theory of intestinal fermentation; however, he did not agree with Baptiste Van Helmont that all physiological processes took place under fermentation. A key contribution of Professor Franciscus Sylvius was that he became the first to describe the digestive ability of saliva and pointed that oral cavity is the first place of digestion. The liquid "saliva" was known before this French scientist, but its digestive function was not previously known [53, 54].

As knowledge increased, there was also continuous progress in all areas of science and digestive physiology had a fair share of the progress in knowledge. As the chemical understanding of the nature of digestion increased, different aspects of digestion including mechanism of movement of food in the intestine and the anatomical structures that regulate this movement became increasingly investigated. The understanding of scientists also grew in the aspect of tissue-level organization of the digestive tract and their functioning. For the first time in 1605, the Swiss anatomist, botanist, and physician, Caspar Bauhin (1560–1624), described the ileocolic valve and correctly explained its function of preventing the intestinal contents from coming back to the small intestine from the colon. So, valves (also called sphincters) were known as anatomical structures that regulate the movement of food substances and release of juice into the intestine in the different regions of the GI tract. Several other valves were also identified in the GI tract. During the first half of the 1600s, the German anatomist, Johann Georg Wirsung (1600–1643), discovered the pancreatic duct in man and showed that it was necessary for the transport of pancreatic juice into the intestine, though details on the anatomy and physiology of the hepatopancreatoduodenal axis were not known [2, 51, 54–56].

In 1654, the Cambridge-trained physician, anatomist, physiologist, pathologist, and colleague of Willaim Harvey, Francis Glisson (1597–1677), reported outstanding findings on one of the large organs of the GI system. After completing his medical degree at the University of Cambridge, and following a period of scientific research and teaching, Glisson was appointed professor of physics in the same university, where he conducted several experiments on the nature of things. His deep interest in medicine made him conduct many experimental studies on the human body, particularly on the organ of the GI system—the liver. His investigation on the liver is still considered as one of the most detailed studies of the human liver in the modern period. Hence, the liver fibrous sack is named after Glisson [2, 51].

Apart from the large glands of the gut (liver, pancreas, gallbladder, salivary glands), scientists began to identify glands that were much smaller in size and located in the mucosa of the intestinal tract. Duodenal glands were identified and described by the Swiss physician, anatomist, and physiologist, Johann Conrad Brunner (1653–1727). These glands were later named after the discoverer—Brunner's glands. Brunner's glands are comprised of tubular submucosal glands found in the duodenum, precisely the part, which is above the hepatopancreatic sphincter (sphincter of Oddi). Following the discovery of one of the first minor glands in the duodenal mucosa, another gland type was identified in the intestinal mucosa. In the middle eighteenth century, Johann Nathanael Lieberkühn (1711–1756) reported the observation of mucous glands in the small intestine, which were later called intestinal glands or crypt of Lieberkühn [10, 51]. The intestinal glands were found to have similar functions with duodenal glands. Further details on these glands are discussed in later part of this book.

In the second half of the seventeenth century, the Swiss anatomist, Johann Conrad Peyer (1653–1712), conducted studies that identified groups of intestinal cells, now called Peyer's patches—aggregates of gut-associated lymphoid tissue usually found in the lowest portion of the small intestinal mucosa. These patches will be later identified to be responsible for gut immunomodulatory functions [51]. Details on the immunomodulatory functions of Payer's patches are discussed in Chap. 10.

The foremost contributor to the tissue level of organization of the GI tract was William Harvey (1578–1657). Born in England as the eldest of seven sons of a farmer, Harvey studied arts and medicine at Cambridge University, where he received a Bachelor of Arts degree in 1597 and in 1602 earned his medical degree from the medical school at Padua, Italy. His younger brothers became London merchants. On receiving his medical degree, William Harvey returned to London to practice medicine and also conducted research [57, 58]. He wrote on human organs in his widely renowned book "Lectures on the Whole of Anatomy," published in 1653. Even though the world knows him mainly on his outstanding work on cardiovascular physiology, this far-famed physiologist was the first to describe the layers of the intestines as tunics, comprising of fibers, flesh, parenchyma, veins, arteries, mesenteries, and mucous. His estimate showed that the intestines were about six times the length of the human body [57, 58].

Pioneer fields (e.g., iatrochemistry, iatromechanics) that directed the flow of knowledge in chemical and mechanical levels of functioning in GI physiology received substantial progress as a new discipline, iatrophysics, which was applied to further explain the mechanisms of GI functioning. Outstanding iatrophysicist scientist in the emerging field of digestive science included René-Antoine Ferchault de Réaumur (or just René de Réaumur) (1683–1757), a French physiologist who showed that digestive chemicals played a huge role on the processes of digestion. De Réaumur isolated gastric juice and demonstrated that digestive secretions could digest meat outside of the body. This discovery not only confirmed the work of Eberle, but also opened the way for future nineteenth-century scientists to investigate the protein digestibility in the digestive tract, which will later lead to the discovery of digestive enzymes. De Réaumur's book on digestion in birds printed in 1752 unraveled many secretes of digestion. As an iatrophysicist, De Réaumur believed that digestion was the result of churning process induced mechanically by the muscles of the stomach wall [51, 59]. Rather than explaining digestion in chemical terms alone, De Réaumur viewed the process of digestion as physical and chemical.

Albrecht von Haller (1708–1777), an eminent Swiss anatomist, physiologist, and student of Herman Boerhaave, published the first textbook of physiology in 1747 in the city of Berne, Switzerland. He later published some volumes of *Elementa Physiologiae Corporis Humani* (Elements of Human Physiology). The text also contained a description of digestion incorporating previously known concepts [2, 51, 60]. As a supporter of iatrochemical school of thought, he wrote in his book that acid in the stomach was produced from the degradation of food. He also spelt out the fact that bile was produced from the liver. Further, von Haller mentioned that bile was important for fat digestion [61]. Even though von Haller realized the importance of secretory activity of the GI tract, he was intellectually handicapped to discuss the matter [62, 63]. Besides digestion, von Haller made contributions to future understanding of the nervous, circulatory, and respiratory systems. He acknowledged the tendency of muscle fibers to contract when the attached nerve is stimulated. In the absence of nerve stimulation, no contraction took place. Thus, he showed that only nerves can transmit sensation [60]. In this same year that von Haller's Elementa Physiologiae was printed, Fredericus Bernardus Albinus (1747–1770), the younger brother of Professor Bernhard Siegfried Albinus (1721–1745), showed that all swallowed substances are transported into the stomach via the esophagus [12], a confirmation of views that was previously identified by other scientists.

The teacher and mentor of von Haller, Hermann Boerhaave (1668–1738), a Dutch physician and pathologist, was one of the most famous physicians of the eighteenth century, teacher and modernizer of medical education and a follower of the school of thought of Hippocrates [64–66]. Boerhaave in 1724 was the first to describe life-threatening non-iatrogenic spontaneous esophageal perforation and the rupture which usually occurs in the left postero-lateral wall of the lower one-third of the esophagus that subsequently formed mediastinal sepsis. His observations were based on his personal clinical and autopsy investigation. This pathological condition is now called Boerhaave's syndrome [64, 67]. Boerhaave's syndrome is barogenic rupture and results from a rapid rise in intraluminal pressure in the distal esophagus. The syndrome is characterized by forceful vomiting, pain, dyspnea and shock. Bleeding occurs but is not usually massive. Barogenic rupture is one of the causes of esophageal perforation. About nine out of ten cases of esophageal rupture usually occur in the anatomically weakest point of the esophagus—the lower one-third and in the left lateral position. The average length of tear is usually about 2.2 cm, lying 3–6 cm above the diaphragm [64]. Some authors even argue that Boerhaave's investigations represent the birth of pathological physiology, the branch of physiology or medicine that deals with the mechanisms of disease development [62]. In 2006, Adams and coworkers [68] published a work and proposed that the name of the Dutch countryman, Baron Jan Gerrit van Wassenaer heer van Rosenberg (1672–1723), from whom the first report of esophageal rupture was made, be incorporated into Boerhaave's syndrome (Boerhaave-van Wassenaer's syndrome). This suggestion may be arguably correct and, though, yet to receive wide recognition.

This era of history was marked by substantial advancement of science as certain procedures that were previously feared and even considered a taboo, which led to the loss of numerous lives, were performed with great success. The modern period had progressive knowledge improvement compared to the period of Renaissance. Many ailments of GI tract were treated with success. Notably, during the eighteenth century in Greece, GI stomas (artificial connections of the gut to the skin; stoma is derived from the Greek word, "stomat," meaning "mouth"), colostomies, designed to relieve digestive obstruction were largely used in surgical operations to treat inflammatory bowel, hepatobiliary obstructions among other conditions. Gastric stomas were introduced to decompress the gut or to deliver food substances [69].

By the mid-end of eighteenth century, the Italian philosopher, Abbe Lazzaro Spallanzani (1729–1799), who became a chemical physiologist and pioneer in modern experimental biology, had produced many diagrams of human digestive system, in which he accurately showed the digestive tract and associated organs. In the middle eighteenth century, he published many scientific papers. Spallanzani was a reductionist, as he believed that many phenomena in nature (including humans) could better be explained in physical or chemical terms. Apart from other areas of science, he notably contributed to respiration. To test his numerous hypotheses that he had formulated, at one time he used animals and another time conducted experiment on himself by swallowing sponges, porous bags, and tubes (note that nowadays there are ethical principles formulated by Research/Ethics Committee of an established institution, based on guiding principles of the Helsinki Declaration that regulate experiments on animals or humans or their tissues). Spallanzani was fortunate to have recovered some of the items he had previously swallowed from his feces or vomitus. Spallanzani reportedly documented the action of saliva in digestion. He correctly showed using his "classical experiment" that gastric juice was responsible for the chemical breakdown of food substances. This renowned Italian scientist showed that gastric juice contains acid that was produced by the stomach itself and not from drinking excess acidic or spar water and did not flow from any other organ or system. As a great physiologist at the time, he proposed that the action of stomach juice on food was due to acid fermentation, not putrefaction or vinous fermentation. Thus, Spallanzani's suggestion was somewhat in conformity with Van Helmont's earlier proposal on the chemical physiology of digestion; however, it later became clearer that Spallanzani's views were incorrect. Spallanzani suggestion that fermentation occurred in the stomach and that it was due to the presence of an acid was not correct as the stomach could have not been necessary for the fermentation process. However, he rightly reasoned and showed that rather than being a process of putrefaction, digestion was a fermentation process. Frankly, during the process of digestion, some processes of fermentation also take place especially in the large intestine and it is carried out by the gut microbiota. Thus, he was able to show experimentally with results indicating that digestion was a chemical process. Another important discovery led by Spallanzani revealed that gastric juice with HCl was responsible for coagulating milk to form "curdled milk." However, it was not certain whether rennet (rennin), pepsin, the acid itself, or another substance in the juice was the agent responsible for the milk coagulation. Following the work of Spallanzani, numerous scientists and experimental researchers started to confirm the results of stomach acid investigations on animal models [9, 59]. Rennin (also known as chymosin) is a member of the aspartic protease family of enzymes. Rennin is an enzyme complex produced by the fourth stomach chamber of cows, called abomasum, gastric chief cells of infants, *Escherichia coli* (*E. coli*), *Kluyveromyces* (formerly *Saccharomyces*) *lactis* (*K. lactis*), and *Aspergillus niger var awamori*. In the presence of pepsin, rennin functions to curdle or coagulate the casein in milk and break the milk into a liquid or semisolid substance, allowing a longer residence in the bowels and consequently better absorption. Rennin is produced in its inactive form known as prorennin. Prorennin is activated by pepsin 1 or 2 [70]. The pH also plays a critical role in this activation. Different components of rennin have their varying activity levels at varying pH [71–73]. Because of the milk clotting and proteolytic activity of rennin, some components of rennin have been successfully produced in the industries to be used in the production of cheeses [73]. There are now available recombinant chymosin and pepsin for cheese making [74]. Milk is the emulsion of fat globules and suspension of casein micelles in water. It contains certain substances (casein) that stimulates, on ingestion, HCl secretion in the stomach, which activates prorennin to convert to rennin. Milk proteinases plasmin and cathepsin D are also bound into micelles. Milk contains the caseinogen protein that includes kappa-casein, beta-casein, alpha-casein, and gamma-casein molecules [75, 76]. Caseins (beta-casein, alpha-casein) are involved in catalyzing the interaction between calcium and milk which is necessary for precipitation and the subsequent absorption of milk. Kappa-casein affects the precipitation of milk. Kappa-casein is the substrate for chymosin. The enzyme, chymosin, cleaves the peptide bond between amino acid residues 105 (phenylalanine) and 106 (methionine) to produce calcium phosphocaseinate. When the specific linkage between the hydrophobic (para-casein) and hydrophilic (acidic glycopeptide) groups of casein is broken, the hydrophobic groups unite and form a network that traps the aqueous phase of the milk. Chymosin acts to extensively precipitate and curdle milk [77, 78].

In 1777, Edward Stevens (ca. 1755–1834), then a medical student in Edinburgh, who arrived from West Indies, performed experimental investigations as part of the criteria for award of the degree and title "physician." His thesis for the degree award involved an experimental description of the isolation of gastric juice from a dog's stomach and the subsequent action of the juice on food substances. In one of his experiments, Stevens placed meat into the gastric juice and after several hours he found that the meat had softened, whereas the meat did not soften when it was placed in water for the same number of hours. He had discovered that gastric juice can digest meat. However, the agent and mechanisms involved in these actions of the gastric juice will continue to remain a challenge for physicians and scientists for some years to come [79].

In 1832, Johann Nepomuk Eberle (1798–1834), a physician from Würzburg, Germany, found that an acid extract of gastric juice that he collected from mammals dissolved protein foods—egg white and meat. This finding was documented in his new book. At this point, it was clear that the agents necessary for digestion were present in the gastric juice. So, there was confusion about the actual agent in the juice that was able to digest the protein substances. The acidity of the gastric juice was clearly known; so many scientists thought that the digestive properties of the juice may be due to the acid content. Because many scientists did not believe in the theory of ferments, and the theory gradually faded away. Obviously, Eberle was not a follower of the theory of ferments. In a further experimental observation made by Eberle in the same year, he noted that HCl in vitro did not digest proteinous substance, but natural gastric juice did similar to the digestive properties of an acidified extract of gastric mucosa. This observation obviously indicted that a non-acid digestive component is present in the juice [80, 81]. But the task was to identify this non-acid component of gastric juice that was responsible for digestion. In a subsequent experiment, Eberle produced a concentrated solution of pepsin using the technique of alcohol extraction of the mucosa. By this method of enzyme extraction, Eberle was able to identify the substance in gastric juice that softens meat or dissolved egg white. Importantly, he also extracted pancreatic protease, which he utilized in his experiments. This German scientist could be regarded as the father of modern chemical physiology of digestion. Interestingly, he further observed using fatty substances that pancreatic juice was responsible for turning fat into a very finely divided state "known as emulsion." This pioneer scientist in GI mucosa physiology, Eberle, believed pancreatic juice aided digestion of fat and its absorption in the intestine. By this contribution, Eberle singled himself out as a modern physiologist who not only using techniques that were considered contemporary at the time, to validate the digestibility of gut juices, initially claimed to be due to the presence of ferments [2, 51, 80, 81].

In the previous year, before the publication of Eberle's book, Erhard Friedrich Leuchs (1800–1837) had first reported the starch digesting properties of saliva. By 1833, two French chemists, Anselme Payen (1795–1871) and Jean-François Persoz (1805–1868), working in a French sugar factory, discovered that alcohol precipitate of malt extract converted starch into sugar. They named the substance responsible for the conversion "diastase" and suggested it to be an enzyme. The two scientists later suggested that the last three letters of diastase "ase" be appended to the root that indicated which substance was been acted upon by the enzyme. The name "diastase" is derived from the Greek "diastasis," meaning a separation. This is because when beer mash is heated, the enzyme causes the starch in the barley seed to transform into soluble sugars and hence resulting in the separation of the husk from the rest of the seed. Diastase refers to a group of enzymes that hydrolyzes carbohydrates; they include α-, β-, and γ-amylases. The term "enzyme" was not introduced at the time of its discovery. The term was later coined in 1876 by Wilhelm Friedrich Kühne (1837–1900) [82, 83]. In a paper which Kühne presented to the Heidelberger Naturhistorischen und Medizinischen Verein (Natural History and Medical Association of Heidelberg, Germany) on the February 4, 1876, Kühne suggested that non-organized ferments called enzymes were responsible for the proteolytic activities of the intestinal (pancreatic) juice [84]. The word "enzyme" is derived from the Greek for "in yeast" or "leavened." The term "enzyme" was later applied to all ferments, not only those of yeast or other unicellular organisms, but also ferments of higher organisms, as their ferments were very similar.

At this time, even though it was increasingly known that GI juice softened starch, fat, or meat, nobody knew how it came about, and besides, while glucose was known to be probably a product of starch digestion, it was not clear the products of action of gastric juice on meat or the products of action of intestinal juice on fats. Glucose was discovered by the German chemist Andreas Sigismund Marggraf (1709–1782) in 1747, but the name "glucose" was actually given by the French chemist, Jean Baptiste André Dumas (1800–1884) in 1838 [2, 3, 51]. Before the discovery of the enzyme that break down starchy food, glucose was yet to be discovered, so it was difficult to think that the sweetened products obtained following addition of saliva or intestinal juice into starch were the hexoses of which glucose was a probable candidate.

The same situation applies to proteins (meat) and their cleavage products—amino acids. While it was reported by the German physiologist Eberle as early as 1832 that gastric juice dissolved protein foods such as egg white and meat, the intermediate or end products of the reaction were yet to be identified. Not many scientists were aware of these monomers. Moreover, it was quite difficult at the time for some researchers in the area of digestive physiology even to suspect that digestion of proteins resulted in monomers such as those already discovered. The first amino acid was discovered as early as 1806 by the French chemists Louis-Nicolas Vauquelin (1763–1829) and Pierre Jean Robiquet (1780–1840) who successfully isolated the compound in asparagus; hence, they named it "asparagine," the name of the amino acid. It should be noted that at the time there was not even a fair knowledge of amino acids in the scientific community. Not many scientists even knew about protein or the composite units of this macromolecule. The term "protein" (from Greek "proteios," meaning "primaries," i.e., the primitive or principal or the first position or rank as it appears as the most important nutrient needed by herbivores) was introduced just in 1838 by the Swedish chemist, Jons Jakob Berzelius (1779–1848). Though a few scientists including the Dutch chemist, Gerardus Johannes Mulder (1802–1880), must have had a fair knowledge of this macromolecule, at this time of history, virtually nothing was known concerning its building or composite blocks. Berzelius reportedly had series of communication with Mulder, which suggested that Mulder had a fair understanding of what proteins were during the time. Moreover, Berzelius's letter to Mulder meant that the Swedish chemist must have known of his Dutch counterpart earlier and probably read one of his papers on protein. Furthermore, in one of the reply to Berzelius, Mulder noted that proteins were important for the maintenance of chemical metabolism. So, arguably, protein was discovered by both Berzelius and Mulder. Subsequently, series of investigations carried out by different laboratories in the