

REVIEW PAPER

FAMOUS BOOKS IN THE HISTORY OF PATHOLOGY

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Key words: history, pathology.

Although there are many texts from the Greek, Roman, and Arabic periods in our history referring to diseases, books describing pathological investigations were not published until the early 16th century. Five authors and their books stand out because they were key to our current understanding of disease. They undermined the humoral theory of Hippocrates and Galen and were the first to show that organs were the site of a disease, later that diseases originated from certain tissues in an organ, and finally that single cells in those tissues were the origin of the problem. In order of appearance, the following five books are selected for this article.

De Abditis Nonnullis ac Mirandis Morborum et Sanationum Causis (1502)

The first of these books was written by Antonio Benivieni [1]. Born in 1443 in a Florentine family as the oldest of five sons, he obtained his scientific education in Pisa and Siena. There are no records of his study, but he must have finished his training around 1470. Benivieni was a physician in Florence for his whole professional life. One of the hospitals he worked in was probably Santa Maria Nuova, the hospital where Leonardo da Vinci (1452-1519) performed anatomical dissections. Da Vinci writes about an old man who passed quietly away in his hospital bed, and he wrote, "I did an autopsy on him to see the cause of such a quiet death". It is not unlikely that Benivieni and da Vinci met, and maybe they discussed their cases.

From various records it is clear that Antonio Benivieni was the author of many medical manuscripts. However, his most famous work is *De Abditis Nonnullis ac Mirandis Morborum et Sanationum Causis* (*About some hidden but miraculous causes of disease and*

cure), in which he accurately described the diseases of his patients and of the autopsies that he performed on them with permission of the families (Fig. 1). After his death in 1502, his brother Geronimo discovered the notes *...wherein he (Antonio) had diligently and minutely set down noteworthy events and useful pieces of knowledge encountered in thirty-two years of years of medical experience. Struck by their novelty and variety, I felt it my duty to put together these (160) unpolished and hurriedly written fragments.* With the help of a good friend, the philosopher and physician Giovanni Rosati, they selected 111 cases. The letters that both men wrote to each other are included in the book. The 49 cases were omitted, were fortunately later found and studied. The significance of this work, as the first book using autopsies in the search for the causes of disease, cannot be underestimated. Being the first physician describing autopsies as a normal and accepted procedure, Antonio Benivieni can be

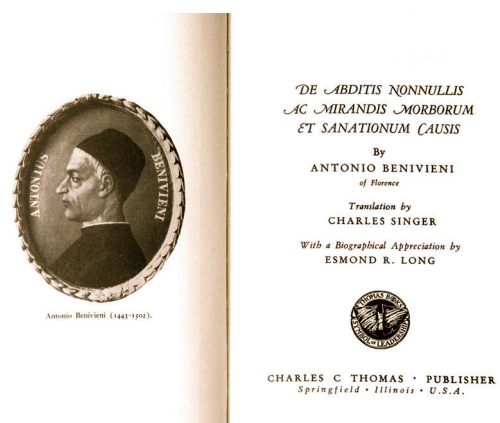


Fig. 1. Antonio Benivieni and the 1954 English translation of his book (property of the author)

considered as one of the founders of pathology as a science. Also, the fact that he wrote this book more than 50 years before Vesalius published the first human anatomical study (*De Humani Corporis Fabrica*, 1543) makes his achievement even more remarkable. Relying heavily on Galen, it was virtually impossible to make correct interpretations and diagnoses at that time, but Benivieni did what he could. Some of the most interesting cases are described as stones in the coating of the liver (probably cholelithiasis with cholecystitis), a mesenteric abscess, severe abdominal pain (probably a colon carcinoma), a heart found covered with hairs, (probably fibrinous pericarditis), and a hardening of the stomach (probably a carcinoma/linitis plastica), the latter described as follows: *My kinsman, Antonio Bruno, retained the food he had eaten for too short a time, and then threw it up undigested. He was most carefully treated with every kind of remedy for the cure of stomach trouble, but as no any use at all, his body wasted away through lack of nourishment, till little more than skin and bone remained. At last he was brought to his death. The body was cut open for reasons of public welfare. It was found that the opening of his stomach had closed up and it had hardened down to the lowest part with the result that nothing could pass through to the organs beyond, and death inevitably followed* (From the English translation of this work by Singer and Long, 1954).

Antonio Benivieni died on November 11, 1502 at the age of 59 years. He is buried in the church of Sanctissima Annunciata in Florence.

Sepulchretum sive anatomia practica ex cadaveribus morbo denatis (1679)

The second book is from 1679, written by Theophilus Bonetus (1620-1689). Relatively little is known about his early life. Born in Geneva on March 5, 1620, he decided quite early in life to become a physician. Before he obtained his medical degree in 1663 in Bologna, he had already travelled extensively throughout Europe, making thorough notes of whatever he saw, heard, or read. He did the same while practicing medicine, first in Geneva and later in 1656 as a city physician in Neufchatel. He returned to Geneva in 1666. Here he had an accident, and from that moment on he gradually lost his hearing and became deaf around his 50th year. He had to give up his medical practice due to this handicap, but his scientific output profited from this unfortunate situation. Bonet was clearly a scholar, knowledgeable in ancient and contemporary medical literature, with special interest in pathological anatomy. This

resulted in his magnum opus of 1679: *Sepulchretum sive anatomia practica ex cadaveribus morbo denatis. Proponens historias et observationes omnium humani corporis affectuum, ipsorumq(ue), causas reconditas* (*Burial vault/cemetery or anatomical studies on bodies affected by disease. An explanation of the histories and observations of all diseases affecting the human body and disclosing their hidden causes*) (Fig. 2). A remarkable book in a time when the humoral theory of Galen still dominated medical thinking. In 1700 (11 years after Bonet's death) there followed a revised edition by Johannes Jacobus Mangetus. The book has over 450 references and is based on more than 3000 post-mortem protocols, many of which were commented on by Bonet. The book is arranged in "Observationes" *de capite ad calcem*, but misses, as also seen in Benevieni's work, correlations of pathological findings and symptoms.

One of his cases is about a girl with "Cachexia, Anasarca, and Leukophlegmasia". *This report concerns a seven-year-old girl who had shown signs of 'obstruction' in the lower abdomen, evidenced by swelling and firmness of the abdomen and scanty urine. There was a 'low' fever, headache, with swelling of the face, and pallor, followed by pulmonary 'catarrh' on lying down, serous vomiting, swelling of the hands, and blackish thick urine. Convulsions supervened and she died. The mother, who had had severe headaches in the past year and whose young son seemed to be suffering from the same disease, wanted an autopsy.*

The abdomen contained much serum, in which the intestines were floating. The stomach and intestines were swollen with gas. The liver was very large but entirely natural in colour and configuration. The spleen was normal. The kidneys were three times the normal size; the interior showing no defect, the outside entirely destitute of fat, and of varied colour. Since from these {findings} the cause of death was not known, the thorax was also incised. The remaining

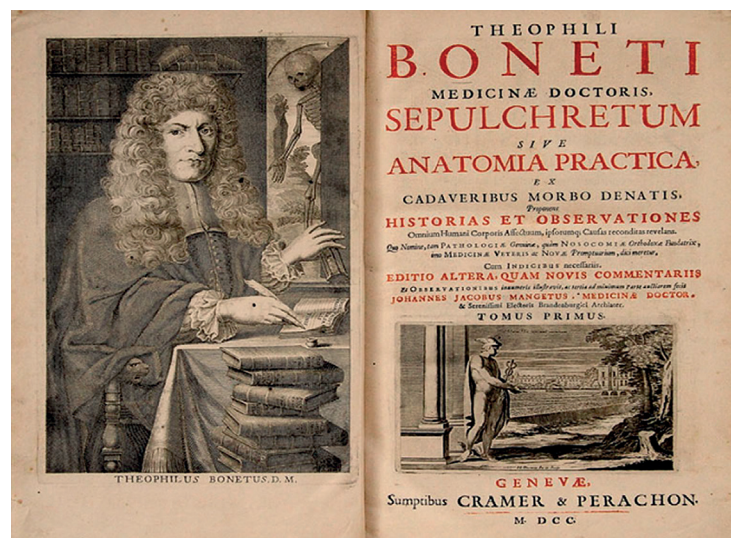


Fig. 2. Theophile Bonet and the frontpage of this book (property of the author)

findings may be summarised: The thorax contained much fluid; the lungs showed 'hardening' (scirrhus) of the right upper and left lower parts; The heart was larger than normal, with abundant fluid in the pericardium; black clot lay in the right ventricle, like a worm. The head was not opened because time was pressing. Again, no diagnosis in this (renal?) case.

This extensive study describes probably every recorded disease from the ancient Hippocratic literature up to Bonet's time. Among the names of many famous physicians are Bartholin, Fallopius, Harvey, Malpighi, Paracelsus, Vesalius, Willis, and numerous others. The cases are collected in anatomical sections and subdivided in symptomatic sectors. Book I deals with diseases of the head, book II with those of the thorax, book III with abdominal diseases, and so on.

Bonet expressed his own feelings about his book as follows: *This work has cost me much more fatigue and care as the reader will draw advantage from it, but I hope I shall receive thanks for taking the first step in a career so eminently useful.* And thanks he got! The real merit of the book is that it is a publication of the forgotten works of others, now made available for later research. The deficit of the lack of an organised correlation between abnormalities and disease, cannot be blamed on him, because medical knowledge at that time did not permit this. This work influenced medicine and medical knowledge until 1761, the year of the publication of Morgagni's *De Sedibus et Causis Morborum*. That book made Bonet's writings obsolete. Bonet died in his hometown Geneva, two days before his birthday in 1689. Good outlines of his life and career are found in the papers of Buess [2] and Irons [3].

De Sedibus et causis morborum per anatomen indagates (1661)

This book, the most famous of all, is written by Morgagni, born in 1682 in Forli, Italy [4, 5]. Morgagni lost his father in his childhood. At the age of 16, he moved to Bologna to study medicine and philosophy, where he became a pupil of the famous professors Hipolyto Albertini (1662-1738) and Antonio Valsalva (1666-1723). As a student, Morgagni was very interested in the study of anatomy and he performed many anatomic dissections with and for Valsalva. He even served as demonstrator or lecturer when Valsalva was traveling abroad. The close relation between both men was probably the most important reason for Morgagni's interest in scientific work. He communicated about his anatomical work to the Academia degli Inquieti in Bologna,

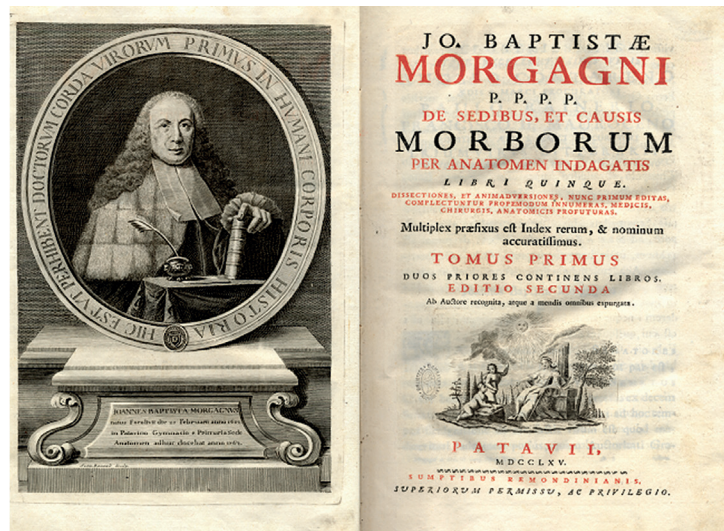


Fig. 3. Giovanni Battista Morgagni and the front page of his *De Sedibus...* (with permission of Biblioteca Gambalunga, Rimini, Italy)

of which he became the youngest member and some years later its president. He published the substance of his communications to the Academy in 1706 under the title *Adversaria anatomica*, the first of a series of five books by which he became famous throughout Europe as a brilliant anatomist; the first book included *Observations of the Larynx*, the *Lachrymal Apparatus*, and the *Pelvic Organs in the Female*.

However, his most important book is his *De Sedibus et causis morborum per anatomen indagatis* (About the seats and causes of diseases, by anatomical investigation) (Fig. 3), published in 1661, when he was 79 years old. This book became the foundation of modern anatomical pathology and one of the most important books in the history of medicine. The title of his book is a summary of its message. Morgagni firmly believed that it was impossible to explain a disease by the completely speculative theory of four invisible humours. He relied primarily on the dissection of the patient's body to reveal the anatomic origin of diseases, then correlating his observations with the patient's symptoms and signals. By the time Morgagni read the *Sepulchretum* written by Bonetus, it became obvious to him that the book had serious flaws. He found in Bonetus' work misquotations, misinterpretations, and inaccurate observations. It lacked an adequate index, making information retrieval almost impossible.

Morgagni later wrote about his initial plan to revise Bonetus' book: *I remember, likewise, that as young men are generally presumptuous enough to entertain thoughts of the most difficult and laborious undertakings, I did not even then despair, but if I should have sufficient leisure in future time, I should not only be able to supply the deficiencies that I have pointed out in the Sepulchretum, and others besides these, but also that I should be able to reform*

the indexes; and I even thought of a plan whereby this might be done, and communicated my plan to that respectable society, which is now called the Academy of Sciences (and previously the *Academia degli Inquieti*) [6]. This may be evidence that he started to collect the material for *De Sedibus* when he was about 20 years old. However, his original project turned up in an entirely new work, based on careful clinical descriptions, most of which involved patients dissected by himself or by Valsalva. His book was the result of his sound background as a practicing physician, his fabulous anatomical experience, his knowledge of the physiology of the time, and his attention to detail. Finally, when publishing *De Sedibus*, Morgagni was already the famous old Professor of Padua, admired for vast scientific achievements and for his integrity. It is no coincidence that his books carry his picture surrounded by the text: *Hic est ut perhibent doctorum corda virorum primus in humani corporis fabrica* (This man is in the opinion of learned men the most knowledgeable person in the field of human anatomy {free translation by JvdT}). The book introduced the concept that diagnosis, treatment, and prognosis of diseases must be based on clear understanding of the pathologic changes in the organs, as the seats of disease.

Morgagni organised *De Sedibus* in 70 letters written to a young man that he met during his work. Morgagni described him as being “much given to the study of the sciences, and particularly to that of medicine”, but never revealed his identity. Morgagni organised the letters into five parts: Book one, disorders of the head; book two, of disorders of the thorax; book three, of disorders of the belly;

book four, of surgical and universal disorders; and book five, of such things as may be added to the former books. The book is extensively indexed and signalled the end of an approximately 1500-year period of domination of the humoral theory of disease. It is not a surprise that many famous people after him were inspired by his work. Among them is Rudolph Virchow, who gave in 1894 in Rome an extensive lecture about Morgagni’s anatomical concept [7].

Traité des membranes en general (1799)

Marie-François-Xavier Bichat [8, 9, 10] (Fig. 4A) was born in Toirette, France, in 1771, the year that Morgagni died. His father was a physician. He studied in Nantua and Lyon, where he devoted himself also to mathematics and physical sciences, but he finally chose medicine, especially anatomy and surgery. Here he was discovered by the famous surgeon Marc-Antoine Petit, head of surgery at the Hotel Dieu in that city. In 1793 he went to Paris, where he came under the supervision of Pierre Joseph Desault (1738-1796). Bichat witnessed and was shaped by the French Revolution, as an army doctor. He used his connections during the French Revolution to obtain permission to investigate the fresh bodies of those who were guillotined.

Bichat developed himself into the father of histology. He submitted tissues to the action of various chemicals and physical conditions, such as boiling, freezing, putrefaction, and desiccation. In this way, without recourse to the microscope, but with ordinary lenses, he was able to distinguish twenty-one

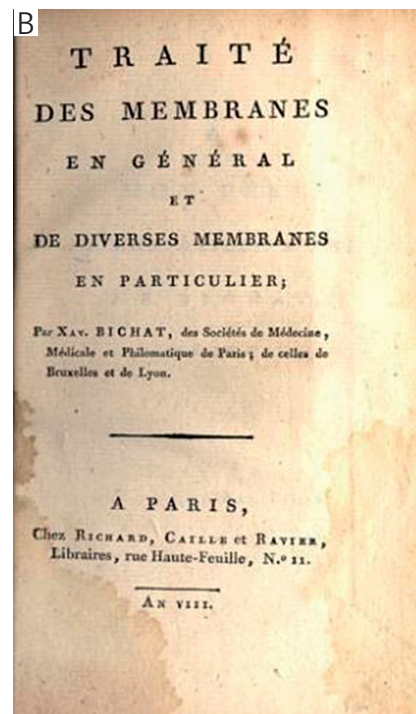


Fig. 4. Marie-François-Xavier Bichat (A) and the title page of his book (B) (public domain)

different tissues, improving the foundation for tissue-based disease.

In his book *Traité des membranes en general* (1799, Fig. 4B), he states: *All animals are an assemblage of different organs. These are in turn made up of many textures of many kind. Just as chemistry has its simple bodies, so anatomy has its simple tissues which make up organs.* Bichat's discovery revolutionised medicine. *We must consider disease not from the standpoint of the compound organs..., but from the standpoint of their different textures, which are almost always attacked separately.* Diseases were no longer simply organ-based abnormalities, but they originated in a larger all-embracing concept of tissues.

Bichat died young, at the age of 30 years, probably due to tuberculous meningitis after falling from the stairs. His discoveries were pursued by his famous student, René-Théophile Hyacinthe Laennec (1781-1826), a great pulmonary pathologist, who carried forward Bichat's ideas on the nature of tissues, and by another Frenchman, Gabriel Andral (1797-1876), who published in 1828 his *Précis d'Anatomie Pathologique* in two volumes, the first on general pathology and the second on special pathology.

Die Cellularpathologie (1861)

This book made Virchow [11, 12] famous. He was born on October 13, 1821, in Prussia (Poland) and studied medicine and chemistry in Berlin at the Prussian Military Academy from 1839 to 1843. When he graduated in 1843, he became the assistant of the famous physiologist, anatomist, and botanist Johannes Peter Müller (1801-1858) at the Charité Hospital. At the Charité, he learned also microscopy with the anatomist Robert Froriep (1804-1861). Froriep was the editor of a journal that specialised in foreign work, allowing Virchow to know the modern scientific ideas from France and England. In 1848, Virchow became Froriep's successor as professor.

Virchow was politically very engaged and is credited as founder of social medicine [13]. In his opinion, physicians had to promote the progress of the lowest social classes. He investigated an epidemic of typhus in the poverty-stricken area of Upper Silesia and wrote the "Report on the Typhus Outbreak of Upper Silesia" (1848), wherein he clearly indicated radical actions to support the advancement of the entire population, through the establishment of democracy and the improvement of education, freedom, and prosperity. When he experienced political discrimination at the Charité in 1849, he decided to accept the chair of pathological anatomy at University of Würzburg. During his six-year period there, he concentrated on his scientific work, including detailed studies on venous thrombosis and his cellular theory. By 1856, Virchow was asked to return to the Charité Hospital

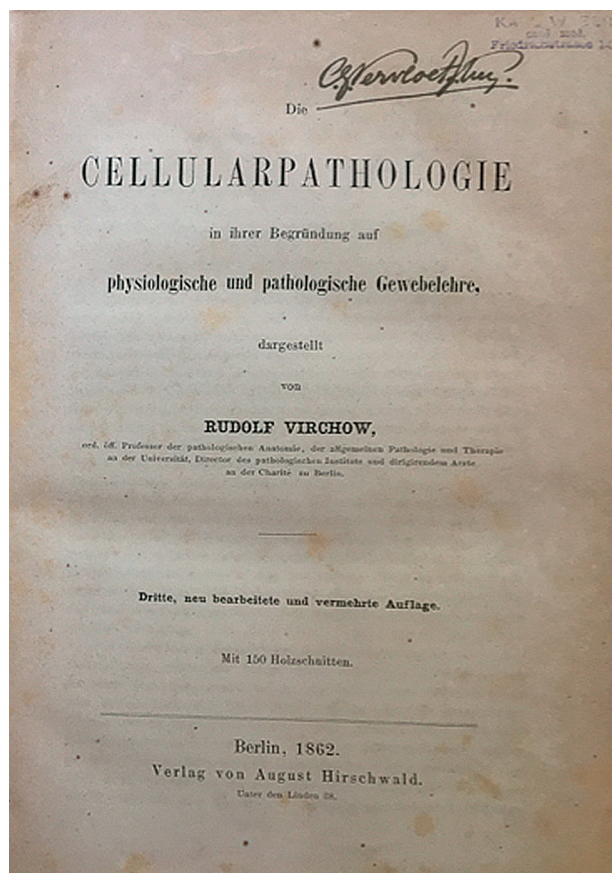


Fig. 5. Rudolph Virchow (A, public domain) and the title page of his *Die Cellularpathologie* (B, property of the author)

in Berlin. Here he became Director of the Pathological Institute, a position he would hold for the next 20 years.

Clinical observation, animal experimentation (to determine causes of diseases and the effects of drugs), and pathological anatomy, particularly at the microscopic level, were Virchow's fundamental principles of investigation: the cells, observed through the microscope, were the basic unit of the body that had to be studied to understand disease.

Hence, Virchow is best known for his cell theory, which built on the work of Theodor Schwann. Accordingly, the concept of the origin of the cells from pre-existing cells was another of Virchow's popularised theories, although the first scientist to carry out such experiments was Francesco Redi (*Omne vivum ex ovo*). Actually, Virchow was one of the first people to accept the work of Robert Remak, who showed that the origin of cells was the division of progenitor cells. Indeed, Virchow elaborated the ideas of Remak in the epigram *Omnis cellula e cellula*, published in 1858, but previously coined by François-Vincent Raspail. Virchow did not include the motto in the first edition of his book on *Die Cellularpathology* (Fig. 5A, B), but in the second edition, where it appears in a slightly changed form: *Where a cell arises, there a cell must have previously existed (omnis cellula e cellula)* [14].

From 1880 to 1893, he was a member of the Reichstag, working on improvement of the health-care conditions for the Berlin citizens. Berlin honoured him with the inauguration of the largest hospital in the city, which bears his name. His eightieth birthday, October 13, 1901, was celebrated worldwide, being a tribute to him by the international scientific community. Virchow died on September 5, 1902 of heart failure after an accidental fall.

The author declares no conflict of interest.

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General reading

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