

A Note From History

The First Printed Case Reports of Cancer

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Antonio Benivieni, an Italian physician, Theophilus Boneti, a Swiss physician, and Giovanni Battista Morgagni, an Italian physician, pioneered postmortem examination for finding hidden causes of diseases. By correlating the results of their clinical and postmortem examinations, they established the foundation of anatomic pathology, clinical medicine, and oncology. *Cancer* 2010;116:2493-8. © 2010 American Cancer Society

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Hippocrates (460-375 BC) is credited with the observation that to study correctly what has been written is an important part of the art of medicine. In remembering Hippocrates' remark, one should also be cognizant that from the time the Sumerians introduced cuneiform writing around 5000 BC in the region of the Tigris and Euphrates rivers, and the Egyptians originated stylized picture-writing in 3000 BC, until Hippocrates' time, there was very limited writing on medicine. After completion of the Roman alphabet, which evolved from the Greek alphabet, in the first century AD, writing was made simple. The handwritten texts of 2 famous Roman physicians, Celsus (25 BC to AD 50) and Galen (AD 130-200) were distributed throughout the then known world. Both books were standard texts, in handwritten copies, for 15 centuries.

In 1450, the German printer Johannes Gutenberg (1395-1468) invented movable type printing. Printing became an industry, and handwritten ancient texts began to appear in printed forms. More importantly, medical notes, case reports, and scholarly texts of contemporary physicians and surgeons were distributed in printed book form using the standardized Roman alphabet. There being no medical periodicals, interesting and unusual medical cases were published in bound volumes or printed in books together with related or unrelated observations.

The first printed case report of cancer was published in 1507 in a modest 54-page book. The book contained 20 autopsy reports and 100 clinical records. The cases belonged to Antonio Benivieni (1443-1502). The cases were collected and published after Benivieni's death by his brother in 1507.¹

Benivieni (Fig. 1), a practicing physician and surgeon in Florence, was an original thinker and a pioneer autopsy pathologist. He made limited postmortem examinations by incision with the intent of gaining knowledge about the hidden internal causes of clinical symptoms and death. He described intestinal perforations, mesenteric and intrathoracic abscesses, cholelithiasis, and a case of pyloric obstruction with callus-like thickening of the stomach. Benivieni's brief and sketchy description of thickened and nodular gastric folds with firm indurations of the stomach, causing complete obstruction of the pylorus, clearly refers to carcinoma of the stomach, although he did not recognize it as such. The patient was a man and a relative of Benivieni. He treated the patient with medicaments for vomiting and wasting without any benefit.

Benivieni's small book signaled the beginning of a stream of postmortem observations. By the end of the 16th century, autopsy examination of deceased patients became routine procedure.

Benivieni's text was translated into English by Charles Singer in 1954.

Theophilus Boneti (1620-1689), a Swiss physician (Fig. 2), collected records of hundreds of postmortem examinations that were performed by his contemporaries or earlier physicians and surgeons. Many of the prosectors were illustrious individuals: Bartholinus (1616-1680) of Denmark, Eustachius (1524-1574) of Rome, Fallopius (1523-1563) of Modena, Fernel (1497-1558) of France, Glisson (1597-1677) of England, Malpighi (1623-1694) of Rome, Meibomius (1638-1700) of Germany, Paracelsus (1493-1541) of Switzerland, Peyer (1653-1712) of Switzerland, Vesalius (1514-1564) of Belgium, and Willis (1621-1675) of England. A few cases recorded by Hippocrates and Galen were also included.

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Figure 1. Antonio Benivieni (1443-1502).



Figure 2. Theophile Boneti (1620-1689).

In 1700, 11 years after Boneti's death, the amassed material, including 2806 cases, was published as a treatise in 3 volumes containing 2260 oversized (9 × 15 in.) pages.² The volumes are divided for diseases of the head, chest, and abdomen and miscellaneous conditions. Each of the 2806 autopsy reports begins with the highlighted final pathological diagnosis and proximate cause of death. Next are the clinical history and autopsy findings. The case reports range from a few lines to several pages. The post-mortem examinations were not complete autopsies. In most cases, the examination was limited to dissection of certain specific areas and organs.

Boneti included malignant tumors (scirrhus carcinoma, cancer, fungous tumor, and sarcoma) with other debilitating diseases, more or less indiscriminately from the head to the toes. Although he did not identify some of the malignant tumors, his pathologic description is sufficiently clear to reach a conclusion.

Boneti's 3 volumes were never translated from the original Latin, except for a cursory review and translation into English of 2 medical cases and the table of contents.³ Owing to the perplexities of Boneti's style and exceedingly intricate arrangement of cases, this report is not all inclusive; the translation into English is limited to the cardinal parts of Boneti's cancer cases.

Among the intracranial tumors, Boneti reported 2 cases with malignant features. The first case concerns a large, cere-

bellar tumor with glandular appearance. The tumor was located deep in the left cerebellar hemisphere. Short of more precise information, one would favor primary or metastatic malignant tumor. The second case is the case of an adult female who presented with chronic headache and pain in the ears and the eyes. On opening the cranium there was accumulation of fluid, distended ventricles of the cerebrum, and a substantially enlarged solid pineal gland. The enlarged noncystic pineal gland should be viewed either as pinealoma or pineal germinoma.

Boneti described 4 malignant tumors in regions of the head. The first case was a destructive scirrhous (carcinomatous) tumor of the nasopharynx with intracranial extension. The second case was an ulcerated scirrhous (carcinoma) of the nose with odoriferous smell. In the third case the patient was an elderly man with an enormous tumor of the chin. The tumor invaded the maxilla. It cannot be answered with certainty whether the lesion was a salivary gland tumor or a squamous carcinoma. In the fourth case, the patient was a 5-year-old girl who presented with a fungous (soft) tumor of the right eye. After a short period of observation, a similar tumor was detected in the left eye. Both tumors invaded the meninges with adhesion to the brain. Boneti did not say so, but this youngster must have had bilateral retinoblastoma.

A firm and nodular tumor occupied the anterior neck of a woman. The tumor encircled the larynx, and the vessels

in the neck were surrounded by nodules. It seems this was a thyroid carcinoma with metastasis to the neck.

Both lung carcinomas reported by Boneti occurred in elderly men. The patients presented with chronic cough, bloody sputum, and episodes of chest pain. One patient died because of ruptured aortic aneurism. At autopsy, a scirrhous tumor (carcinoma) of the left lung and multiple firm tumor nodules in the mediastinum were incidental findings. In the other case, the right bronchi were obstructed by a firm mass. The right lobes and the peribronchial glands were studded with firm nodules.

There were 2 breast cancer cases, both diagnosed by Boneti. One patient was a postmenopausal woman who had a neglected ulcerated cancer of the left breast with extension into the pectoralis muscle. At autopsy, fluid and multiple subpleural nodules were found in the left chest. In the other case, a woman died with dyspnea and glandular tumor nodules, resembling mammary carcinoma, in the left axilla, left chest wall, left lung, and left humerus. The breast was not dissected, because there was no palpable tumor. Having no palpable intramammary tumor, it is a conjecture that the tumor was infiltrating lobular carcinoma.

Boneti described and diagnosed 3 esophageal carcinomas. Patient number 1 was a 56-year-old man who had severe difficulty in swallowing. He was kept on liquid diet. Surgical instrumentation was contemplated when he died. On opening the body, a large cancerous growth was found in the middle part of the esophagus. Patient 2 presented with choking and vomiting. He could not eat or drink. Examination after death showed obstruction of the orifice of the stomach at the esophageal junction. Multiple scirrhous nodules were visible in the liver. Boneti's description is consistent with carcinoma at the esophagogastric junction; however, he failed to recognize the hepatic nodules as metastases. In the third esophageal case, the patient's face was swollen, and the vessels in the neck were distended to the width of a finger. On dissection, a firm tumor was found in the upper third of the esophagus. The tumor was ulcerated and perforated into the lower neck and the mediastinum. It is interesting that Boneti gave a fairly perfect first description of superior vena caval syndrome.

Boneti diagnosed 1 of the 2 cases of gastric carcinoma. In the case he diagnosed, there was a tumor with cartilaginous consistency at the pylorus. The tumor caused nearly complete obstruction of the pyloric orifice. The patient was a 35-year-old man in the case he failed to diagnose as carcinoma. The patient was kept on various medications for indigestion. After death, the wall of the entire stomach was found thickened. Outside of the stomach, egg-size firm

nodules were visible. It seems the case was *linitis plastica* with metastasis.

Boneti was accurate in his description of clinical signs and symptoms as well as pathologic findings in a carcinoma of the right colon and 2 cases of rectal carcinoma. The abdomen and pelvis were not explored.

The liver was found massively enlarged in 3 cases. The diaphragm was elevated to the extent that the right lung was compressed. Two patients were middle-aged men. Both livers were enlarged with globoid masses of fleshy, thymus-like appearance. The described tumors can best be classified as hepatomas. The third patient with enlarged liver was an infant. The liver was extremely large and was filled with globoid masses. The diagnosis in this case will never be known, because the dissection was limited to the liver. However, metastatic neuroblastoma and Wilms tumor would be high on the list of possible primaries.

Two patients presented with back pain and abdominal tenderness. No medication helped, and both patients died within months. On opening the abdomen, the pancreas was found to be indurated and nodular with multiple scirrhous nodules. The peripancreatic tissues and the liver contained similar tumor nodules. Boneti did not state his diagnosis, but both cases appear to have been carcinoma of the pancreas with metastases.

The mayor of Rome, an obese 43-year-old man, died with bilious (yellow) complexion after many years of indigestion and pain under the right ribs. On autopsy, the most pertinent finding was thickening of the choledochus from the liver to the duodenum, with complete obstruction of the distal end by a scirrhous tumor. The gallbladder was distended without stones, and the liver was dark in color. Apparently this patient had carcinoma of the common bile duct.

Renal tumors were found in the body of 2 adult patients. One tumor was a head-size, encapsulated, noncystic, solid mass in the left kidney. One would consider renal cell carcinoma or oncocytoma. The second patient had a papillary polypoid tumor in the distended pelvis of the right kidney. The kidney itself was atrophic, and the renal parenchyma was partly destroyed by the tumor. The described tumor was obviously an urothelial carcinoma of the renal pelvis.

Among the uterine carcinoma cases, there were 2 cervical carcinomas. Both tumors were ulcerated and detected on vaginal examination at advanced stages before death. Two additional cases were polypoid uterine fungus (soft cancer) in postmenopausal women. Both tumors were traced to the enlarged endometrial cavity. It was pointed

out that the myometrium was thin and partly destroyed by the infiltrating tumors. One polypoid fungus extended downward and protruded out of the vagina. This was perhaps a mesodermal mixed tumor. In connection with this case, Boneti inserted a note that he had seen a similar polypoid soft cancer in the vagina of a young girl. He must be referring to botryoid sarcoma. The fifth uterine tumor occurred in a 30-year-old woman who presented with uninterrupted uterine bleeding after delivery. At autopsy, the uterus was filled with solid and soft hemorrhagic globular masses. The uterine wall was eroded, and multiple soft globules were found in the pelvis. Boneti admitted that he never seen anything like this before. One can only conclude that the patient had a form of gestational trophoblastic disease.

In 2 cases of bladder carcinomas, the clinical presentations were fairly typical, and scirrhus cancer was suspected in both cases. On dissection after death, the bladder of 1 patient was filled with a fist-size scirrhus tumor, and the other patient's tumor destroyed the posterior wall of the bladder and invaded the rectum, creating a vesicorectal fistula.

Boneti did not diagnose the 2 prostate cancers, but his pathologic description is sufficiently detailed to render diagnosis. In both patients, the enlarged, firm, and nodular prostate obstructed the urethra to the extent that the urethral catheter could not be passed. In 1 case the scirrhus firmness extended into the bladder neck, and in the second case there were periprostatic firm nodules.

Upon dissection, in 4 cases Boneti characterized the pathologic findings as abdominal carcinomatosis. The patients were adults. In 1 case the spleen was so large that it was held up by the pubic bone. One would think of leukemia or extramedullary hematopoiesis.

Three patients in their teens presented with enlarged neck nodes and respiratory difficulties. They were treated with oral medications without any improvement. As their disease progressed, firm nodules were palpated in the axilla and the groins. Necropsy examination showed tumor nodules in the retroperitoneum and the mediastinum. On cut section, the nodules were fleshy in appearance. Boneti concluded that the patients died with non-necrotizing nodular strumatosi (lymphoma).

In addition to the above-reviewed 43 cancer cases, Boneti's book² is a storehouse of original observations on benign tumors. The cases range from pituitary adenoma, meningioma, optic neuroma, thyroid adenoma, and bronchocele to uterine and colonic polyps, synovial cysts, synovial chondromatosis, and osteochondroma. Some of the new terms Boneti introduced are papillomatosis, carcinomatosis, stru-



Figure 3. Giovanni Battista Morgagni (1682-1771).

matosis (lymphoma), carcinoids (small carcinomas), miliary distribution (spreading), deep venous thrombosis, parenchyma, and cellular tissue (fat).

The third person who reported cancer cases in print is Giovanni Battista Morgagni (1682-1771), professor of anatomy at the University of Padua (Fig. 3). He was a wealthy practitioner of medicine. His patients were drawn from the ranks of bishops, cardinals, nuns, and important businessmen. Morgagni's text *De Sedibus*⁴ was published in 1761, when he was 80 years old. In its 1325 pages in 2 volumes, Morgagni correlated clinical and postmortem findings in 700 autopsied cases. He published the first description of mitral stenosis, angina pectoris, endocarditis, hepatic cirrhosis, and congenital jaundice. He recognized periosteal exostosis (osteochondroma) and intramedullary exostosis of long bones (osteoma or osteosarcoma). He knew about malignant ascites and routinely performed paracentesis. Morgagni studied and reported 17 cases of cancer. However, his understanding of cancer was severely handicapped by not recognizing metastasis even when he saw it.

Five cases of cancer reported were in the stomach. Three of the patients were men in their 50s and 60s; the 2 women were 40 years of age. The patients presented with chronic indigestion, epigastric pain, vomiting, and general malaise. Shortly before death, 1 patient with palpable

Table 1. Chronology of Events

Year	Medical history	Year	World history
1507	Benivieni publishes his <i>De Abditis</i>	1507	The word America introduced as a geographic designation
1541	Paracelsus, the first chemotherapist, dies	1541	De Soto discovers the Mississippi River
1543	Vesalius' <i>Fabrica</i> printed	1546	Steamboat designed in Spain
1561	Fallopian describes the uterine tubes	1564	Galileo and Shakespeare born
1628	Harvey discovers the circulation of blood	1626	New Amsterdam, today's New York, founded
1645	Fernel introduces the terms <i>physiology</i> and <i>pathology</i>	1643	Newton discovers gravity
1653	Bartholin discovers the thoracic duct	1654	Portuguese drive the Dutch out of Brazil
1666	Scultetus illustrates removal of cancerous breast	1666	Stradivari makes his first violin
1667	Hook introduces the term <i>cell</i>	1682	Halley predicts the return of a comet every 76 years
1700	Boneti's <i>Sepulchretum</i> printed	1707	Great Britain formed by the union of England and Scotland
1721	Leuwenhoek illustrates squamous cells	1716	The first lighthouse in America built in Boston Harbor
1741	Andry coins the term <i>Orthopedie</i>	1743	Thomas Jefferson born
1759	Astruc's <i>Treaté des Tumors</i> printed	1754	First golf club founded in Scotland
1761	Hill cautions about the use of tobacco	1756	Mozart born
1761	Morgagni publishes his <i>De Sedibus</i>	1760	Russians occupy and burn Berlin

tumor vomited gastric fluid containing soot-like material. He passed per rectum similar black material (occult blood). The tumors of the men were scirrhous and were prepyloric in location. Morgagni traced the tumors in the 2 women to the gastric glands and described firm white nodules about the size of small grapes in the liver. He pointed out that in 1 patient the supraclavicular nodes also contained white nodules (Virchow nodes).

Three patients had carcinoma of the pharynx and the larynx. One of the pharyngeal tumors occurred in a young man. On dissection, all 3 tumors were large and ulcerated scirrhous growths. Two patients had firm nodules in the lateral neck.

A 60-year-old man and a 50-year-old woman had chronic constipation and abdominal pain. The situation progressively worsened, with abdominal distention and wasting. On postmortem examination, the man had nearly complete obstruction of the transverse colon by a large scirrhous tumor. In the case of the woman, the lumen of the rectum was diminished by a firm cancerous mass. The wall of the rectum was firm and nodular.

On opening the abdomen of a 60-year-old man, Morgagni found an enlarged firm pancreas. The head of the pancreas pressed on the duodenum and caused partial obstruction. Morgagni felt that the pancreas was carcinomatous and warned that because of the deep location of the pancreas, pancreatic tumors are seldom diagnosed during the life of the patient.

Two middle-aged women had intermittent vaginal bleeding and lower abdominal pain for longer than a year. On vaginal examination, both patients' uterine cervix was firm and ulcerated and gave foul smell. The diagnosis of

cervical cancer was rendered. Days before the patients died, their abdomens distended with fluid. Some of the fluid was drained, and according to Morgagni, it tasted salty. After death, dissection of the uteri and pelvic organs confirmed the clinical diagnosis of cervical cancer. In both cases the cancer invaded the bladder neck, and there was distention of the ureters.

Morgagni's clinical presentation of 2 patients about 50 years old is quite unique. Both patients had unilateral axillary nodularity and soft swelling of the corresponding arm (lymphedema). The patient with the left axillary problem was found to have a substantial tumor in the left breast. After months of compression of the breast with concave lead plate, her condition did not improve, and the mammary tumor was excised (lumpectomy). On examination after death, the left breast, the left chest wall, and the left axilla were found to be infiltrated by cancerous tumor nodules. In case of the patient who had her tumor in the right axilla, the breast was not dissected after death, because no tumor was felt in the breast. Despite dissimilarities in mammary findings, Morgagni concluded that both died with breast carcinoma. He traced the swelling of the arms to accumulation of fluid in the cellular adipose tissues because of compression of vessels and nerves in the axilla by cancerous growth.

A man had pain in the back and abdomen for several months. He gave a history of indurated and enlarged left testis. The pain became intolerable and he died by wasting. On postmortem examination, his posterior abdomen (retroperitoneum) on the left side, was filled with fleshy and firm globoid tumor nodules from the kidney to the public ramus. Morgagni found puzzling that the tumor nodules connected downward with the enlarged left testis. Apparently,

Morgagni failed to connect the tumor (germ cell tumor) in the left testis and the retroperitoneal tumor nodules (metastasis).

A 15-year-old boy presented with enlarged nodules in the neck and axilla. After he developed nodules in the groin, his condition rapidly deteriorated, and he died by emaciation. The body was examined by complete autopsy. The whole body was filled with pigeon egg-size white and fleshy nodules. Morgagni had no diagnosis, but it is apparent that the patient had a type of lymphoma.

Morgagni's book was a medical bestseller for decades. It was translated into English by B. Alexander in 1769.

In conclusion, the road was long and arduous from the time of the first public dissection of a human body in 1315 to the 16th century, when postmortem examination of patients became routine practice (Table 1). Benivieni, Boneti, and Morgagni pioneered postmortem examination for finding hidden causes of diseases. By recording and publishing the results of their examinations, they established the

foundation of anatomic pathology and clinical medicine. Furthermore, correlating clinical signs and symptoms of 61 cancer patients with autopsy findings, Benivieni, Boneti, and Morgagni laid the groundwork for oncology.

CONFLICT OF INTEREST DISCLOSURES

The author made no disclosures.

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