Roentgenologic Examination of the Gallbladder (Cholecystography)
The Article That Launched a New Era of Radiology

SUMMARY OF THE ORIGINAL ARTICLE
Roentgenologic Examination of the Gallbladder: Preliminary Report of a New Method Utilizing the Intravenous Injection of Tetrabromphenolphthalein
Evarts A. Graham, MD, and Warren H. Cole, MD
JAMA. 1924;82(1):613-614.

Organic phenolphthalein compounds had previously been injected intravenously into rabbits and dogs and observed to be concentrated into bile fluid. Graham and Cole identified a compound (the calcium salt of tetrabromphenolphthalein) that when given intravenously to patients resulted in “definite and cleanly cut shadows of the gallbladder” in radiographs of the abdomen obtained a few hours later.

Their preliminary results suggested that a normal gallbladder is usually visualized, while a pathologic gallbladder is more difficult to observe, and predicted an important diagnostic role for this new roentgenologic examination.

See www.jama.com for full text of the original JAMA article.

Commentary by Ronald G. Evens, MD
IN 1924, GRAHAM AND COLE PUBLISHED A CLASSIC JAMA article1 with a goal of improving the surgical diagnosis of abdominal disease by a novel method of imaging the gallbladder (cholecystography or the Graham-Cole test). They were successful and at the same time, they stimulated a new era for the clinical use of the Roentgen ray, a technology that continues today with the promise of molecular imaging.

In the 1920s, radiologic imaging was in its infancy (Roentgen’s report of the “invisible ray” appeared in 1895) and the use of imaging was confined to anatomical findings—primarily of the chest and extremities, with an increasing use of barium as an “opaque meal” for gastrointestinal examinations.1 Graham, chair of surgery at Washington University School of Medicine and an internationally recognized academic surgeon because of his leadership of the Empyema Commission during World War I, understood the importance of basic science research to clinical medicine. While attending a meeting of physiologists, he became aware of an observation of John J. Abels that phenolphthalein, a cathartic (still marketed today under the brand name of ex-lax) administered to dogs by mouth, was absorbed from the gastrointestinal tract, concentrated by the liver, secreted into bile fluid, and stored in the gallbladder.2

Graham returned to St Louis and assigned Cole, one of his best surgical residents, to the project. Cole became a great academic surgeon in his own right,3 leading the Department of Surgery at the College of Medicine, University of Illinois at Chicago for 30 years. Graham also asked for advice about how to image a chlorinated phthalain (by attaching a halogen—eg, iodine, bromine) and sought the help of a good friend and industrialist, Edward Mallinckrodt, owner of the Mallinckrodt Chemical Works of St Louis, who assigned one of his best chemists to the project of finding a method of imaging the gallbladder.

Graham and Cole then spent many months injecting a variety of compounds into dogs and x-ray imaging canine abdomens hoping to visualize the gallbladder. Their efforts were unsuccessful; however, one of the dogs receiving the injections had an easily identifiable gallbladder on the radiograph of its abdomen. Several days of repeated injections, trying to reproduce this observation, failed. The entire team in the research laboratory was called together and a key observation was noted by the animal diener that the one success was in a dog that he had neglected to feed the morning of the experiment. The importance of administering the contrast agent (as it is now identified in clinical medicine) while the animal was fasting allowed the successful imaging of the gallbladder to be reproduced.

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The transfer of this observation to patients required further analysis of a variety of compounds with consideration for patient safety, proper dosage, imaging criteria, and the resulting classic publication in JAMA.1

Graham's accomplishments continued after 1924 and included performing the first successful pneumonectomy for lung cancer and being among the first to identify cigarette smoking as a cause of lung cancer. He was a pioneer leader of American surgery and medicine who chaired the American College of Surgeons and the American Board of Surgery and was a founding member of the Joint Commission on Accreditation of Hospitals. Graham died of lung cancer and his first pneumonectomy patient survived him.4

Commercialization of a pharmaceutical product was the result of testing more than 89 chemical agents by Mallinckrodt Chemical Works and by 1930, the visualization of the gallbladder became an important part of imaging, radiology, and clinical medicine. Progress included the development of a contrast agent that could be administered by mouth, rather than by injection.

The article by Graham and Cole1 revolutionized the diagnosis of abdominal pain and other symptoms suggesting biliary or gallbladder disease. Imaging of the gallbladder became a standard. In the late 1960s, assignment to a busy gastrointestinal fluoroscopy service included a daily schedule of performing 20 or more upper gastrointestinal examinations and gallbladder evaluations with the patient receiving several pills and fasting on the night before the early morning of the imaging study. Cholecystography became one of the most accurate radiologic examinations (deriving many true positive results and very few false positive ones).3

In addition, the article by Graham and Cole1 initiated several activities of fundamental importance to medicine and medical care. This publication was the first report of progress from integration of knowledge from physiology, chemistry, imaging, and clinical science by dedicated physicians to satisfy a clinical need. Soon after this publication, a variety of imaging contrast agents were identified that allowed imaging of the genitourinary system and the vascular system, and the field of interventional radiology began. The advancement of diagnostic imaging methods continued with the development of clinical useful isotopes in the field of nuclear medicine and continues today with the development of the field of molecular imaging.6

In 1924, the department of surgery at Washington University included radiology as a division of the department. Graham recognized diagnostic imaging as more than an interesting technology, leading many efforts in the development of imaging/radiology as a science and as a clinical specialty in American medicine. He not only supported the formation of a radiology division at Washington University, but he encouraged the General Education Board of the Rockefeller Foundation (directed by Abraham Flexner of Flexner Report fame) to endow an institute of radiology. However, because none of the endowed funds could be used for bricks and mortar, Graham obtained a gift from Mallinckrodt to build an 8-story building for imaging that is still used as part of the Mallinckrodt Institute of Radiology at Washington University.7

This 1924 preliminary report is a JAMA Classic, with great significance to clinical medicine and to future innovative research and development.

It is ironic that the Graham and Cole “new” technology for medicine and radiology (contrast agents, cholecystography) has been replaced by another newer technology (ultrasound) in the diagnosis of gallbladder disease.8

Indeed, time, science, and technology all march on.

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REFERENCES