1974

A short history of diagnostic radiology

Bert David Collier Jr.
Yale University

A SHORT HISTORY OF DIAGNOSTIC RADIOLOGY

BERT DAVID COLLIER, JR.

1974

YALE

MEDICAL LIBRARY

A Short History of Diagnostic Radiology

Bert David Collier, Jr.

1974

A Dissertation Presented to

the Faculty of the Medical School of Yale University

in Candidacy for the Degree of Doctor of Medicine.

A Short History of Diagnostic Radiology[1]

I. Introduction.

Shortly after Roentgen[2] announced the discovery of x-rays in January of 1896, x-ray technology began to be used for visualizing broken bones and locating foreign objects within the human body. In May, 1896 John Cox at McGill University reported on patients referred to him for x-ray examination.[3] Included in this series are a bullet in the brain of a child, a broken hip, a drainage tube which had been lost in a lung, a fractured skull, kidney stones, and demonstration of a cavity in the lungs. All of these cases except the lung cavity involved x-ray visualization of dense objects against a less dense background.

Professor Cox's equipment consisted of photographic plates and a Crookes x-ray tube. During a roentgen ray examination, x-rays from the Crookes tube readily passed through air, were absorbed only in part by muscle and fat, and were most completely absorbed by dense objects such as bones, calcified kidney stones, or bullets. The x-rays which had passed through the patient's body went on to expose a photographic plate.

John Cox was among those pioneers in radiology who correlated x-ray findings with normal and pathological anatomy. The nineteenth century physician with only a minimum of experience in interpreting chest x-rays was able to identify the x-ray opaque shadows of the heart, spine, and ribs. Within a few years, skilled observers had correlated

the x-ray picture of lung cavities, apical scarring, and a raised hemidiaphragm with advanced pulmonary tuberculosis. In 1896 the x-ray examination rarely revealed more than the normal anatomical distribution of air, soft tissues, and bones. Later it was learned that otherwise invisible organs could be visualized during x-ray examination if they had been filled either with air or with x-ray opaque barium. For example, a barium meal gives the stomach a bone density which stands out against the soft tissues of the abdomen.

During the past eighty years, radiology has developed a great number of diagnostic procedures. Today, x-ray examinations of the chest, brain and spinal cord, heart and vessels, gastrointestinal tract, biliary tract, urinary tract, and skeletal system have become reliable and safe aids to diagnosis and management. Of the many organ systems examined by x-rays, each of which might be a separate chapter in a comprehensive history of radiology, only x-ray evaluation of pulmonary tuberculosis and of the biliary tract are dealt with in this short history.

Along with being employed in diagnostic procedures, x-rays have been used for treatment of both benign and malignant disease. In addition, many of the diagnostic procedures of nuclear medicine either complement or compete with diagnostic radiology. However, neither nuclear medicine nor the therapeutic use of x-rays has approached the significance of diagnostic radiology in attacking the major diseases of the twentieth century. Therefore, these closely related topics will be omitted.

II. Pulmonary Tuberculosis and Diagnostic Radiology.

Introduction

Before 1896 and x-ray examination of the chest, diagnosis and evaluation of pulmonary tuberculosis centered around three factors: a history of cough, night sweats, and weight loss; certain characteristic findings on inspection, palpation, percussion, and auscultation of the chest; and identification of tubercle bacilli in the patient's sputum. The manifestations of TB which the physician can demonstrate at the bedside were common knowledge by the last decade of the nineteenth century. In fact, the description of TB's signs and symptoms in William Osler's famous textbook, The Principles and Practice of Medicine (1892)[4] is virtually identical with Harrison's modern text, Principles of Internal Medicine (1970).[5] Surpassing our contemporary medical textbooks in accounts of the more advanced and terminal stages of tuberculosis, Osler's 1892 text clearly outlines the progression of bedside findings over the natural course of this disease.

By appropriate staining and microscopic examination of the sputum, the physician of 1892 could accurately identify Mycobacterium tuberculosis, the infectious agent causing pulmonary tuberculosis. Osler correctly emphasizes the value of such sputum examination when stating that, "The bacilli give an infallible indication of the existence of tuberculosis and may be found in the sputum before the physical signs are at all definite."[6]

Osler (1892) mentions the use of Koch's tuberculin as a treatment for tuberculosis. However, this use of tuberculin (a form of

killed tubercle bacilli) was soon dropped and a new application found. Tuberculin came into use as a skin test which would identify those individuals who had been infected with tubercle bacilli. In 1901 Osler states, "During the past few years it [Koch's tuberculin] has been employed extensively at Johns Hopkins Hospital both on the medical and surgical sides with the most satisfactory results, and, so far as I know, without harmful effects."[7]

However, the tuberculin skin test yields only a yes-or-no answer to the question, "Has this patient experienced TB?" The skin test reveals nothing about the current state of the patient's lungs. On the other hand, x-ray studies of the chest allow the physician to see the early changes of pulmonary TB, the scarring patterns indicative of quiescent disease, and cavity formation in the more advanced states of pulmonary tuberculosis.

If Roentgen's discovery was to become a mainstay of the early diagnosis of pulmonary tuberculosis, skills in interpreting x-ray studies and improvements in technique and equipment were essential. First, consider the challenge in interpreting the x-ray plates. The light and dark shadows seen on the plates had to be correlated both with the normal anatomy of the chest and with the progressive changes from the early through the terminal states of pulmonary tuberculosis. Full utilization of the information on x-ray plates required that radiologist be able to differentiate between pulmonary tuberculosis and bronchogenic carcinoma, asbestosis, emphysema, and numerous other diseases of the lungs. In addition to expertise in interpreting x-ray studies, improvements in apparatus, materials, and technique have

enhanced the diagnostic value of chest radiology. Using Crookes tubes, low voltage power sources, and simple glass photographic plates, the radiologists of 1901 were not able to obtain the detail and clarity of today's x-ray films. In addition to the need for more sophisticated equipment and for well established correlations between disease processes and x-ray shadow patterns, time was needed both to train radiologists and to convince the medical profession that this new procedure was a valuable addition to diagnostic methods.

In following the history of diagnostic radiology, reference is made to various editions of Osler's Principles and Practice of Medicine and Harrison's Principles of Internal Medicine. As leading textbooks of their day, Osler's and Harrison's commentaries on the use of radiology reflect authoritative opinions. Aware that medical education and practice were being swayed by their writings, the authors tend toward a conservative and critical approach. This is not to say that hidden in the pages of these medical textbooks is the one correct course which diagnostic radiology has or possibly should have followed, or even that these textbooks represent the greatest expertise available in their day. Rather, Osler's and Harrison's textbooks record the advice of leading clinicians to medical students and fellow practitioners: candid, concise, conservative, widely accepted and forward looking commentary on pulmonary tuberculosis and diagnostic radiology.

Evaluations of the then current x-ray apparatus, materials, and techniques are made for the periods 1896-1913, 1913-1940, and 1940-1973.

Pulmonary TB and Radiology in 1901.

In the fourth edition of Principles and Practice of Medicine[8]

(1901) Osler devotes eighty-one pages to tuberculosis without once mentioning radiology. This omission from a thorough review of TB can leave little doubt as to Osler's evaluation of the current and potential value of diagnostic radiology. The omission also suggests that in cases of pulmonary tuberculosis diagnostic radiology was being employed too infrequently to deserve either critical or favorable mention.

However, radiology had made progress in the five years since Roentgen's discovery. In 1901 Francis Williams of Boston published a remarkably sophisticated and prophetic textbook of diagnostic and therapeutic roentgenology.[9] Williams correctly interprets x-ray findings in pulmonary tuberculosis, emphasizes the unique value of diagnostic radiology in detecting early cases of pulmonary TB, and demonstrates the value of x-ray examination in following cases of pulmonary tuberculosis.

The half-tone reproductions of x-ray plates and the instructive diagrams in The Roentgen Rays in Medicine and Surgery are crude by modern standards. However, Williams correctly interprets the signs of tuberculosis. Commenting on the appearance of the diseased lungs during x-ray examination, Williams writes,

> The apex of one lung is seen on the fluorescent screen to be darker than normal, owing to the increased density of this portion of the lung; and, second, the excursion of the diaphragm is seen to be restricted on the affected side, and usually in the lower part of its excursion. The heart is also often times drawn toward the diseased lung.[10]

Williams places particular emphasis on the value of x-ray examination in early detection of TB. He stresses that x-ray findings of disease may be present before the patient develops cough, weight loss, and night sweats and before the astute clinician can with certainty

detect the characteristic findings of pulmonary tuberculosis on physical examination of the patient. However, Williams emphasizes that diagnostic radiology should be used in conjunction with the patient's history, physical examination, microscopic sputum examination, and skin test in arriving at a diagnosis. Because early diagnosis favored successful treatment through nutrition, rest, and fresh air, Williams points again and again to the importance of x-ray examination when there is any question of TB.

> It is obvious that if the physical signs are slight and the patient is complaining of some other than a pulmonary trouble, the presence of tuberculosis of the lungs in its earliest stages may be overlooked if only the ordinary methods are used. Therefore, in cases which are open to suspicion, an X-ray examination should be made.[11]

In 1901 Williams recognized that x-ray examination could be used to follow the progress of a patient with pulmonary tuberculosis. A series of x-ray plates would unambiguously document the healing or spread of the patient's lung disease. Also, x-ray plates are less sensitive to observer variability than are the findings of physical examinations. Thus, diagnostic roentgenology might provide not only more detailed information but also new dimensions in examination of the lungs. With these points in mind, Williams presented the following outline for roentgenology of pulmonary tuberculosis--an outline which might appear in a textbook of today.

"Classes of Cases of Pulmonary Tuberculosis, in which the X-Ray Examination is of Value. -
- "A. As an Aid in Diagnosis. . . .
- "B. In Old Lesions of Tuberculosis.
- "C. For determining Existing Conditions more Accurately.
- "D. In determining the Progress and Extent of Disease. . . .
- "E. In determining the Extent of Disease. . . .

"F. In Acute Miliary Tuberculosis.
"G. In showing Cavities in the Lungs."[12]

Comparing the opinions of Osler and Williams illustrates an important point: x-ray examination of the chest was a promising diagnostic procedure in 1901, but it had not yet demonstrated the reliability or achieved the wide use necessary to be mentioned among the accepted principles and practices of Osler's textbook.

Pulmonary TB and Radiology in 1912.

X-ray diagnosis of pulmonary TB enters Osler's textbook for the first time in the eighth edition (1912).[12] Only one paragraph is devoted to the subject, much of which is quoted below. While attesting to roentgenology's potential for demonstrating the very early changes of pulmonary TB, Osler points out that other diseases might produce similar changes. He cautions against spurious interpretations of x-ray films and neglect of other diagnostic techniques.

> X-ray-Diagnosis - In skilled hands the study of cases with the Roentgen rays is of great value. . . . In diseased conditions changes are seen in the hilus, shadows due to enlarged or calcified glands and to the increase in the fibrous and lymphatic tissues in the mediastinum. The pulmonary vessels with their contained blood play an important part in the production of the shadow. A study made at the Phipps' Dispensary by Dunham, Boardman, and Wolman showed that in a very large percentage of all the early cases, clinically found to be tuberculosis, these shadows showed certain changes which corresponded to the clinical findings. It is not proven, however, that other pulmonary conditions, such as those produced by the influenza bacillus, may not cause the changes. [As of 1973, such hilar changes in the lungs are not attributed to the influenza bacillus.] The X-rays undoubtedly show very early changes in the lungs, but they can not determine the etiological factor. In the majority of cases the X-rays tell

> no more than a careful clinical examination, and they do not differentiate an active from a healed lesion. More than any others, radiographers need the salutory lesions of the dead house to correct their visionary interpretations of shadow, particularly those radiating from the roots of the lungs.[12]

Osler's succinct comments on roentgenologic diagnosis of pulmonary TB are similar to the opinions of Sherman Bonney, professor of medicine at the University of Denver. In Pulmonary Tuberculosis and Its Complications (1908) Bonney states,

> During the past year, with the valued assistance of Dr. S.B. Childs, I have resorted to radiography in a large number of clearly defined cases of tuberculosis, in order to compare the clinical and skiagraphic findings. This method of diagnosis has been used to confirm, if possible, the results of physical examination with reference to small circumscribed effusions, pulmonary cavities, and suspected mediastinal glands. As a rule, the information secured has been strikingly conclusive. As a result of this inquiry, however, previous convictions as to the slight practical value of the x-ray in diagnosis of very incipient cases without well defined structural lesions [such as effusions, cavities, and raised diaphragms] have been substantially confirmed.[13]

In comparing the opinions of Williams, Osler, and Bonney, note that only Williams (1901) supports roentgenologic diagnosis of early pulmonary tuberculosis. Bonney (1908) correctly interprets what by today's standards are dramatic and unmistakable x-ray findings consistent with pulmonary tuberculosis, but he doubts the value of roentgenology in early diagnosis. Osler (1912) states that both early and late changes can be revealed by x-rays. He emphasizes the need for correlating x-ray shadows, clinical data, and the findings at autopsy before accepting roentgenology as a mainstay of diagnosis.

Part of this divergency of opinion might be traced to the variability of results when using the apparatus, film, and techniques which characterized the Crookes tube or gas tube era of radiology.

Apparatus, Materials, and Technique: The Crookes Tube Era.

For routine examination of the chest, the following criteria provide a performance standard for equipment and technique in diagnostic roentgenology:

1. An exposure to radiation which does not pose a hazard to patients or medical personnel.

2. Control over both the quantity of x-rays emitted from a point source and the ability of the x-rays to penetrate tissues and bones.

3. Total elimination of scattered or secondary radiation so that all radiation reaching the photographic film has traveled in a straight line from a point source.

4. The ability to examine with x-rays those anatomic regions which are obscured in normal x-ray films.

In 1974 this performance standard has not yet been attained. However, the history of equipment and technique reveals a series of closer and closer approximations to this goal.

For the roentgenologist of 1896 typical equipment would have been the partially evacuated Crookes x-ray tube, a power source of the induction coil or static generator type, and photographic plates. Not only would each Crookes tube have its own particular x-ray emission characteristics, but the x-ray output of a particular tube would vary wildly during the exposure of a single photographic plate. A Crookes

tube might be emitting strongly at the start of a plate exposure only to have the output fall off drastically a few minutes later.

As for power sources, the static generator--commonly referred to as a static machine--was capable of generating direct current spurts of high voltage but only low amperage. To achieve higher amperage, the radiologist might turn to induction coils. However, induction coils yielded alternating current whereas direct current was more suitable for the operation of the Crookes tube. The conversion of alternating to direct current was imperfectly handled by rotating wheel interpreters until Clyde Snook's interpreterless transformer (1908) solved the power source problem for diagnostic radiology. In combination with the unreliable Crookes tube, inadequate pre-1908 power sources made the x-ray exposure of photographic plates an art: film detail and clarity varied markedly from exposure to exposure and roentgenologist to roentgenologist. The divergent opinions of Williams, Osler, and Bonney might in part be based upon the quality of x-ray studies in their respective clinics.

During most of the pre-Coolidge tube era, glass plates were employed more widely than photographic film or paper. However, under pressure of increasing volume and the shortages of glass plates during World War I, cellulose nitrate and later the fire resistant cellulose acetate film came into common use. Calcium tungstate screens were another important early innovation. Because x-rays cause calcium tungstate and certain other salts to fluoresce, it is possible to intensify the exposure of an x-ray plate by sandwiching the plate between calcium tungstate screens. This sandwich technique was discovered early

in 1896 by at least three independent investigators in North America.[14]

A number of additional problem foiled the production of clear, detailed, reproducible x-ray plates. Because the Crookes tube did not provide a point source of x-rays, and because scattered and secondary radiation constituted as much as 90 per cent of the radiation reaching the plates,[15] early x-ray plates lacked detail and contrast. In addition, the direct relationship between voltage applied to a Crookes tube and x-ray penetration of soft tissues was not appreciated.

Pulmonary TB and Radiology in 1930.

The eighth edition of Principles and Practice of Medicine (1912) is the last version to which Osler contributed. Thomas McCrae assumed sole responsibility for revisions of the ninth (1920) through the twelfth (1935) editions, after which Henry A. Christian edited the text through its sixteenth edition (1947). The section on x-ray diagnosis of pulmonary TB in the ninth edition (1920) and the tenth edition (1925) is virtually unchanged from the Osler and McCrae commentary of 1912. However, in the eleventh edition (1930) the interesting addition of the qualifying adjective "some" into a sentence which had reamined unchanged since 1912 suggests that radiologists were making valuable contributions to patient evaluation. "More than any others, some roentgenologists need the salutary lessons of the dead house to correct their visionary interpretations of shadows."[16]

Pulmonary TB and Radiology in 1935.

Until McCrae's twelfth edition of The Principles and Practice of Medicine (1935), commentary on x-ray diagnosis of pulmonary

tuberculosis had been confined to one paragraph--a paragraph which remained largely unchanged through the twenty-three years since Osler's eighth edition. In discussing "The Natural or Spontaneous Cure" McCrae (1935) writes, "As to cavities we have had to alter the older views and recognize that healing is possible in a certain number of cases. The X-ray evidence seems conclusive,"[17] McCrae also warns against the erroneous diagnosis of tuberculosis by those not sufficiently trained in x-ray studies and includes the usual one paragraph mention of diagnostic radiology under "Diagnosis of Pulmonary Tuberculosis." Radiology is not mentioned in McCrae's "The Prognosis in Tuberculosis" and "Prophylaxis in Tuberculosis." In the "Treatment of Tuberculosis" section no mention is made of case follow-up with serial x-ray studies.

Apparatus, Materials, and Technique: 1913 to 1940.

Much of the improvement in apparatus, materials, and technique after 1913 and before World War II is embodied in the following list of innovations:

1. the Coolidge tube,
2. the Potter-Bucky grid,
3. radiologic contrast media,
4. laminography.

1. The Coolidge Tube

Surpassing the gas filled Crookes tubes in reliable control over emission of x-rays, the Coolidge tube (1913) revolutionized radiology. No longer was the exposure of x-ray film a high art built upon the peculiarities of a laboratory's Crookes tubes and the science and

superstition of the "grand master" roentgenologist. Thanks to the reliable, point source output of the Coolidge tube, heuristic hunches as to exposure time and tube placement were replaced by precise, well documented standards.

The characteristics of the Coolidge tube can be traced to the use of a hot cathode for electron emission, a modification which confers the ability to operate in a total vacuum. William David Coolidge obtained degrees in electrical engineering from the Massachusetts Institute of Technology and physics from the University of Leipzig before beginning his work on x-ray tubes at the General Electric Research Laboratory. Based on the earlier research of Edison (who demonstrated that a heated filament will supply electrons) and Lilienfeld (who showed that the "Edison effect" will operate in a vacuum), Coolidge's tube produces x-rays by bombarding a target with electrons from a heated cathode.

2. The Potter-Bucky Grid

In 1921 General Electric made the Potter-Bucky grid available as a ready-made item. This "grid" is a series of parallel lead strips designed to absorb scattered radiation. During the exposure of an x-ray film, the parallel lead strips move in mass across the film with the result that any one spot on the film is alternately exposed to x-rays or shielded by lead. The parallel lead strips absorb scattered radiation which would otherwise blur the x-ray images. If the Potter-Bucky grid remained motionless, then there would be parallel, unexposed strips on the film. However, the motion of the grid produces uniform

film exposure and insures that the grid is not visible on the developed film. The Potter-Bucky grid is particularly useful for improving the clarity and detail during diagnostic roentgenology of structures deep within the body.

The striking results of the Potter-Bucky grid amazed radiologists. In The Rays reactions of various gatherings to Potter's new device are recorded.

> Following another radiological meeting, Dr. Potter again displayed negatives made with his moving parallel-strip "grid." One radiologist, he later recalled, turned away from the sharp negatives in anger and announced accusingly, "You've touched those negatives up!" He could not be convinced that so blur-free a negative could be produced with an X-ray tube.[18]

3. Radiologic Contrast Media

Under most circumstances, x-ray examination can not clearly visualize blood vessels, intestines, the gallbladder, and the ventricles of the brain. However, filling these structures either with x-ray lucent air or with an x-ray opaque substance will provide a sharp x-ray image against a background of soft tissues. For this purpose, air, barium, and a variety of halogenated compounds are employed as radiologic contrast media. For example, when a patient swallows a barium sulfate meal, his stomach becomes x-ray opaque. After a barium meal, a stomach ulcer can be identified as a cleanly punched out crater projecting outward from the otherwise smooth curvature of the x-ray opaque stomach wall.

The period after World War I has witnessed an expanding repertoire of contrast media and related diagnostic procedures which enable

the diagnostic radiologist to investigate a wide range of body functions and structures.

4. Laminography

Assume that during an x-ray examination, the Coolidge tube is moved from left to right across a patient's chest while the photographic film moves in a parallel plane from right to left. The geometry of this situation is such that a bone density object equally distant from both the film and the x-ray tube will be clearly visualized on the developed film. However, a bone density object close to either the tube or the film will be blurred and indistinct. Using this laminography procedure, the radiologist can demonstrate anatomy of the lungs which would normally be obscured by overlying or underlying bones. The results of laminography are comparable to surgically removing the bones and taking normal x-ray projections.

The first high quality laminograms were developed by Andrews, Moore, and Kieffer in the late 1930's. Laminography has been used with great advantage for examining small lung cavities, the bones of the middle ear, the upper cervical spine, the temporomandibular joint, and numerous other anatomic sites.

By 1940 significant progress had been made in control of x-ray emission, elimination of scattered radiation, and examination of normally obscured regions. The Coolidge tube provided a well controlled point source of x-rays; the Potter-Bucky grid absorbed much of the scattered radiation; and contrast media and laminography permitted examination of formerly obscured sites. Unfortunately, the hazards of

radiation received too little attention until after World War II.

Pulmonary TB and Radiology in 1938 and 1942.

With the 1938 and 1942 editions of The Principles and Practice of Medicine, diagnostic radiology for pulmonary tuberculosis achieves the status of a crucial and routine diagnostic procedure. In reading these two editions of this textbook, it is obvious that the indications for roentgenologic examination of the chest have been vastly expanded. A larger number of clinical decisions are being made on the basis of the radiologist's report. Writing on "Diagnosis of Pulmonary Tuberculosis," Christian (1938) states,

> The early diagnosis of pulmonary tuberculosis may be said to mean the recognition of lesions which do not give positive signs [i.e. lesions whose presence a physician could not detect on physical examination of the patient]. Suspicion is an important factor in the early diagnosis with a determination to leave nothing undone to decide whether or not tuberculosis is present. X-ray study of the lungs must be made in every suspicious case. . . .[19]

In "Prophylaxis in Tuberculosis" the 1938 edition stresses, "the careful study of all those who have been in contact with patients having tuberculosis, with x-ray examination of each."[20]

While discussing "Prognosis in Pulmonary Tuberculosis" in the fourteenth edition (1942), Christian writes, "If the lesion by x-ray shows evidence of fibrosis, prognosis is enhanced; the reverse is true with caseation and poorly walled off cavities."[21]

In 1942 the discovery of streptomycin, the first drug effective against tuberculosis, was two years off. The outlook for cases of pulmonary tuberculosis hinged upon detection at the earliest possible date.

Treatment regimes emphasized rest, diet, clean air, and symptomatic treatment of temperature and cough. A few selected patients received lung collapse therapy to arrest their disease. Physicians could be hopeful about stopping the downhill course of tuberculosis only in the early, incipient cases. Christian (1942) writes that,

> Since so often the lesion is wide spread before the correct diagnosis is made, and treatment consequently has been begun late in the disease, it can not be expected that prognosis will be other than poor; probably half die within 5 to 10 years. The extent of lesion, when treatment is begun, is of great prognostic import; under very excellent conditions for treatment about 1/4 of moderately advanced and something over half of far advanced cases can be expected to die in a twenty year period.[22]

Thus, in 1942 early detection was the key to successful treatment of pulmonary tuberculosis, and x-ray examination was often the crucial diagnostic test.

Most of Christian's "X-Ray Examination" section is quoted below. For the reader who may still doubt that the diagnostic significance of chest radiology changed between 1910 and 1942, it is suggested that the previously quoted paragraph from Osler's 1912 textbook be read before the following long quotation from the 1942 edition of The Principles and Practice of Medicine.

> X-ray Examination - In skilful hands x-ray examination is of great value. The x-ray undoubtedly shows very early changes in the lungs but can not always determine the etiological factor. The x-ray is not infallible, however, in the recognition of existing tuberculous lesions; some escape the most skilled x-ray examination; 10 to 15 per cent of small tuberculous lesions will be missed (Amberson).
>
> Much depends on the roentgenologist who examines the films; with a skilled man the results are of great value. The estimation of the meaning of

> changes in an x-ray film needs skill, knowledge and good judgment as much as does the estimation of the clinical features. The physician and roentgenologist should examine the films together. In some cases with positive signs and positive sputum the x-ray examination is negative. More than any others, some roentgenologists need the salutary lessons of the dead house to correct their visionary interpretations of shadows. Fluoroscopic examination is of value especially in detecting changes in movement of thoracic contents and in locating lesions, which are to be subjected to some sort of surgical procedure. The photographic method, using a cellulose acetate film, at present gives the clearest records of the tuberculous process and its changes. . . . The recent technique of laminography (tomography, stratigraphy, planigraphy) permits visualization of selected planes and is very useful in localizing cavities and abscesses. Various oblique and lateral views with the patient in different positions help, particularly in the study of the hilar and mediastinal structures.[23]

Apparatus, Materials, and Technique: 1940 to 1974

After 1940, changes in the apparatus, materials, and technique of diagnostic radiology are characterized by new applications, incremental improvements, and automation. Many of these changes were motivated by the post World War II emphasis on safety. Outside the field of nuclear medicine, revolutionary changes in apparatus and materials comparable to the introduction of the Coolidge tube (1913) have not occurred. This is not to say that diagnostic radiology has remained static, but rather that the scientific principles embodied in the apparatus and materials of 1940 are essentially the same principles which underlie the equipment of today's diagnostic radiologist.

Much of the post World War II growth in diagnostic radiology has come through identification of normal and pathological findings for a wider range of diseases and anatomic sites. For example, selective

angiography has developed in the past thirty years through the enhanced appreciation of normal and abnormal radiographic patterns of blood vessels. New equipment has been marketed for use in selective angiography, and the equipment is justified in terms of improved diagnostic capabilities. However, the underlying scientific principles or patterns --for example, injection into vessels of an x-ray opaque substance--have changed very little since 1940.

However, the improvements in apparatus and technique since 1940 have significantly reduced excessive and unnecessary exposure to x-rays. X-ray film quality has improved slightly, and through automation and simplification costs have been held down. The following improvements have been introduced since 1940:

1. Phototimers. In 1944 Drs. Hodges and Morgan introduced a versatile phototimer with the capability of automatically turning-off the x-ray tube at the point of optimum film exposure.[24]
2. Faster x-ray film which requires less patient exposure to radiation.
3. Full developing of x-ray films. With the introduction of automatic film developers, it is possible to insure that films spend an adequate length of time in the developing tank. In as much as under-developing of films encourages over-exposure of patients to radiation, full developing of x-ray films has increased safety.
4. More sensitive fluorescent screens.
5. Adequate filtering of the x-ray beam. Filters absorb low energy x-rays which would not penetrate through soft tissues to reach the x-ray film.
6. High voltage (85 kilovolts or higher) operation of x-ray tubes. This

reduces the production of low energy, low penetrating power x-rays.

7. Redefining the indications for x-ray examinations.

8. Lead shielding and smaller x-ray beams.

9. Image intensifiers for fluoroscopic examinations. Instead of recording the fluorescence of calcium tungstate or other salts on x-ray film, the radiologist may directly observe the x-ray induced fluorescence on a calcium tungstate screen--a technique known as fluoroscopy. Until the introduction of image intensifiers in the early 1950's, fluoroscopy required a relatively high x-ray exposure. Image intensifiers have increased the brightness of the fluoroscopic screen over 1,000-fold. Motion picture filming of fluoroscopic examinations or cinefluoroscopy has followed the introduction of image intensifiers.

Pulmonary TB and Radiology in 1950, 1962, and 1970.

After the sixteenth edition (1947), The Principles and Practice of Medicine was not published again until 1968. Organized along the lines of Osler's textbook, Harrison's Principles of Internal Medicine has been among the successors to The Principles and Practice of Medicine. Harrison's chapters on pulmonary tuberculosis have been written by William Kirby (1950, 1962) with William Stead (1970).

In 1944 the antibiotic streptomycin was isolated and shown to be highly efficacious in treating TB. The discoveries of isoniazid, p-aminosalicylic acid, and additional drugs effective against Mycobacterium tuberculosis followed within a few years. By the middle of the 1950's, a patient with any but the most advanced stages of pulmonary tuberculosis could begin drug therapy with the expectation of total

cure and return to a normal life. Since 1950, the diagnosis of TB has rested upon history and physical examination, tuberculin skin testing, microscopic examination and culture of sputum, and diagnostic radiology.

Kirby (1950, 1962) exhorts his readers not to abandon the bedside search for abnormal breath sounds and tympanic cavities in favor of x-ray examination. Perhaps Kirby was concerned that the availability of several diagnostic procedures and the efficacy of drug treatment had led too many medical students to forego detailed physical examination of the chest. However, after first urging that the physician not forfeit the examination to the radiologist, Kirby lists instances in which the findings on physical examination must be corrected by x-ray examination.

> The widespread use of the x-ray during the past 25 years has demonstrated the marked limitations of physical examination in detecting and appraising the lesions of pulmonary tuberculosis. As a result, the tendency at present in many quarters is virtually to ignore the physical examination altogether; this is lamentable, for physical signs contribute information which, when correlated with the x-ray findings, gives a more complete understanding of the nature and activity of the parenchymal disease.
>
> Early asymptomatic infiltrations are usually missed on routine physical examination, and indeed it is often surprising how extensive the x-ray infiltrations may become before definitive physical abnormalities are detected. . . . Even with large cavities demonstrable on the x-ray, however, the classic signs of tympany and amphoric breathing are often absent because the soft, shaggy cavity walls and surrounding structures do not act as good resonators.[25]

Equally strong support for x-ray examination is found in the 1970 edition of Principles of Internal Medicine. William Stead writes,

"(B)ecause examination of the lungs in the early stages is so frequently unremarkable and the blood count and sedimentation rate are normal, the importance of the chest roentgenogram in diagnosis of tuberculosis cannot be overemphasized."[26]

Before x-ray examination of the chest, physicians relied more heavily upon what might be learned at the bedside. With attention of the nineteenth century physician focused on physical examination of the tuberculous patient, evaluation of the clinical signs and symptoms of pulmonary TB reached its highest level. Osler (1892) places great diagnostic and prognostic import on a meticulous physical examination. For estimating the location and size of tuberculous lung cavities, the following aphorisms are found in Osler's text:

> The pitch of the percussion note changes over a cavity when the mouth is open or closed (Wintrich's sign), or it may be brought out more clearly on change of position.
>
> The cracked-pot sign is only obtainable over tolerably large cavities with thin walls.
>
> In those rare instances of almost total excavation of one lung the percussion note may be amphoric in quality.
>
> In very large cavities both inspiration and expiration may be typically amphoric.
>
> In very large thin-walled cavities, and more rarely in medium-sized cavities, surrounded by recent consolidation, the rales may have a distinctly amphoric echo, simulating those of pneumothorax.
>
> Pseudo-cavernous signs may be caused by an area of consolidation near a large bronchus. The condition may be most deceptive--the high-pitched or tympanitic percusion note, the tubular or cavernous breathing, and the resonant rales, simulate closely those of cavity.[27]

Thus, the physician of 1892 would carry out a detailed examination of the chest with a view toward determining the size, location, and quality of tuberculous destruction. However, today's physician is not even aware of the pearls for examination of the chest found in Osler's 1892 text. In conjunction with modern x-ray studies, a less detailed and imaginative physical examination suffices to uncover the available information without embarrassing overinterpretation of signs and symptoms. Although the Oslerian aphorisms will often connect physical findings with the underlying pathology of tuberculosis, they are crude and unreliable when compared to x-ray examination. Diagnostic radiology has replaced one of the main thrusts of Osler's 1892 textbook.

III. Radiologic Examination of the Gallbladder and Bile Ducts.

Introduction

In following the progress of radiologic examination of the gallbladder and bile ducts, a review of scientific literature is conducted. This method requires placing limits upon both the time period and the literature that is considered. For example, should the finding of gallstones as reported by Marcellus Donatus in the fourteenth century[28] be the start of our literature review even though it has no apparent bearing upon events in this century? The synthesis of chemicals which give the gallbladder an x-ray opaque shadow has been critical to radiology of the biliary track. How deeply should we probe the chemistry literature in our search for critical research events?

Since such limits must be arbitrarily defined, caution is needed in using such a literature review for analytic purposes. Documenting research events does not mean that we can define cause and effect relationships even though such causal relationships may appear most logical and likely when viewed in retrospect. For example, few researchers have read all of the scientific literature relevant to their work, and it often is the case that an experiment's logical extension of previous research work becomes apparent only after the researcher has completed his laboratory work. With these warnings in mind, let us proceed to a review of published literature relating to radiological examination of the biliary track.

In 1924 Graham and Cole produced an x-ray opaque shadow in the gallbladder by the intravenous injection of tetrabromphenolphthalein,[29] a technique which revolutionized radiologic diagnosis of gallbladder disease. An x-ray opaque substance which is concentrated in the gallbladder, tetrabromphenophthalein might either demonstrate x-ray lucent cholesterol gallstone, fail to fill a diseased gallbladder, or by filling a normal gallbladder rule-out disease. The Graham and Cole paper marks a major advance in the reliability and significance of radiologic diagnosis.

Since the Graham Cole paper (1924), advances in gallbladder radiology have centered on improvements in contrast media. In <u>Classic Descriptions in Diagnostic Roentgenology</u> Andre Bruwer states, "The former period [before 1924] may be summarized as the period of technical picture-taking artistry--mixed with a fair amount of wishful

thinking. In 1924 occurred the scientific revolution in biliary roentgenography, and the field has belonged, and rightly so, to the chemist since that year."[30]

In tracing the literature before the Graham and Cole paper, four areas are examined: pathology and surgical treatment, radiologic diagnosis of gallbladder disease before 1924, soluble iodine compounds as radiologic contrast media, and physiology of the gallbladder and phthalein pharmacology.

Gallstones and Infections of the Gallbladder: Pathology and Surgical Treatment.

The surgical treatment of gallstones and infections of the gallbladder has changed very little since 1924. For example, the description of gallbladder surgery in John DaCosta's Modern Surgery[31] (1919) is comparable to the account given in Schwartz's Principles of Surgery[32] (1969). A key point emphasized by both authos is that gallstones and infection occur together. When there is fulminant infection of the gallbladder, gallstones invariably can be found. Conversely, when the gallbladder is full of stones, there is usually some evidence of infection present.

Both authors describe patients with obvious gallbladder disease as having fever, sweating, abdominal pain, and if the common bile duct is obstructed by a gallstone, marked jaundice. When the common bile duct is not obstructed, symptoms may be milder, and reliable diagnosis of gallstones and infection of the gallbladder becomes more difficult.

In The Principles and Practice of Surgery,[33] Herman Haubold

(1922) outlines a procedure for surgical removal of the gallbladder, a cholecystectomy, which is not materially different from the account found in Schwartz (1969). Haubold states a strong preference for cholecystectomy (first performed by Carl Langenbuch (1882)) as opposed to cholecystotomy (opening and draining the gallbladder as was popularized by Lawson Tait (1879)). Haubold indicates that cholecystectomy is a more extensive and demanding procedure than cholecystotomy, but that the advantages of cholecystectomy lie in a more complete search and removal of gallstones along with a very low recurrence of gallstone formation. Haubold's opinion is in accord with the current preference of general surgeons for the cholecystectomy procedure. However, agreement on the indications for cholecystectomy was not universal. In Modern Surgery DaCosta (1919) expresses a preference for the simpler cholecystotomy operation.

None the less, understanding and surgical treatment of gallstones and gallbladder infections have remained remarkably static since 1922. However, although safe and efficacious gallbladder surgery existed in 1922, the diagnosis of gallbladder disease was notoriously unreliable. The accuracy of pre-operative diagnosis of gallbladder disease changed dramatically with the introduction of the Graham-Cole cholecystogram. This new x-ray examination of the gallbladder insured the more appropriate application of surgical treatment. For example, a low grade fever and intermittent pain in the right upper quadrant of the abdomen might be due to a chronic infection of the right kidney or to gallstones and gallbladder infection. Without x-ray studies to rule out gallbladder disease, a patient with chronic infection of the right

kidney might be subjected to a cholecystectomy.

In 1924 much of the uncertainty in diagnosis of gallbladder disease was removed by the Graham-Cole technique. Under most circumstances, a gallbladder which does not fill with the x-ray opaque contrast media will be found at surgery to have a gallstone obstructing its outlet and/or marked infection. A less reliable sign of gallbladder disease is to outline in the gallbladder x-ray lucent gallstones against a background of x-ray opaque contrast media.

In the 1931 edition of his textbook, DaCosta identifies those patients for whom the Graham-Cole cholecystogram is of value.

> Cholecystography has been one of the most notable advances in medicine. . . . The value of cholecystography has been proved beyond question. In disease of the gall-bladder a reasonably certain diagnosis can be made upon history and physical signs alone in about 70 per cent or with the addition of simple radiography and a barium meal, 80 per cent of cases. In the 20 or 30 per cent of doubtful cases, Graham's method is of great value. . . . Cholecystography is correct in a high percentage of cases, and is very accurate in cholecystic disease accompanied by stones.[34]

<u>Status of Radiologic Diagnosis of Gallbladder Disease before 1924</u>

The reliability and significance of radiologic examination of the gallbladder was reviewed by Carman, MacCarty, and Camp of the Mayo Clinic in February of 1924.[35] At this time Russell Carman was an outstanding authority in gastrointestinal radiology, his textbook <u>The Roentgen Diagnosis of Disease of the Alimentary Canal</u>[36] having become particularly influential.

The authors present a series of 343 patients with one or more pre-operative x-ray examinations, subsequent surgical removal of the

gallbladder, and confirmed pathology of the gallbladder in the surgical specimen. Of these patients, 155 or 45% were diagnosed by x-ray examination as having gallbladder disease while 188 or 55% of the cases revealed no abnormalities on x-ray examination.

During this period, radiologists looked for the so-called direct and indirect signs of gallbladder disease. The most reliable direct sign is the visualization of a calcium containing gallstone, but unfortunately only a small percentage of gallstones contain sufficient calcium to be x-ray opaque. A much less reliable direct sign is the faint shadow of thickened walls of a diseased gallbladder. Indirect signs include deformities and spastic contraction of the adjacent portions of the stomach and small intestine.

Having reviewed current radiologic technique and presented their case series, Carman, MacCarty, and Camp concluded that,

> These facts suggest doubt whether a gallbladder demonstrated by the roentgen ray, and with a minimal amount of disease at operation, is respondible for the patient's symptoms. . . . (T)hese series raise the question of whether the results warrant the time and expense required for roentgenologic examination.

There are reports before 1924 of contrast media being accidentally and in some cases intentionally introduced into the bile ducts and gallbladder. For example, Carman (1915) reported a case in which an abnormal communication between the small intestine and the gallbladder allowed swallowed barium to pass into the gallbladder and bile ducts. During radiologic examination, Carman was able to visualize the gallbladder and bile ducts as x-ray opaque shadows.[37] Burckhardt and Müller (1921) used a needle and syringe to introduce both air and x-ray

opaque substances into the gallbladders of cadavers and of living patients.[38] However, the puncture technique of Burckhardt and Müller was too hazardous for routine use.

Thus, before 1924 radiology was an unreliable aid in diagnosis of gallbladder disease. Before Graham and Cole began their research, there were reports of contrast media filling the gallbladder and at least one attempt to develop a clinically useful method of gallbladder visualization by a needle puncture technique.

Soluble Iodine Compounds as Radiologic Contrast Media

The intravenous injection of sodium iodide for x-ray visualization of blood vessels (1919, 1923) and of the kidneys (1923) demonstrated certain principles and techniques which were later applied by Graham and Cole. In particular, the use of sodium iodide as a contrast media was both the first purposeful intravenous injection of an x-ray opaque substance and the first radiologic technique dependent upon the concentration of an x-ray opaque substance by the natural function of an organ. Both of these concepts were later employed by the Graham and Cole technique. Ruth and Edward Brecher point out that,

> It is probable that they were influenced to continue by the success achieved at just this time by their colleague in the department of surgery at Barnes Hospital, Dr. Barney Brookes, whose startling successful visualization of a patient's arteries and veins by means of sodium iodide occurred at Barnes Hospital on September 23, 1923, in the midst of the Graham-Cole experiments.[39]

For many years before the first radiologic use of sodium iodide, patients had been swallowing thick barium pastes which would render their esophagus, stomach, and intestines opaque to x-rays. Because it

passes through the gastrointestinal tract without being absorbed, insoluble and potentially toxic barium could be used for G.I. radiology. However, x-ray opacification of veins, arteries, and various other internal structures required soluble, nontoxic contrast media. A prerequisite for an x-ray opaque contrast media is that it contain an element of high atomic weight such as barium, iodide, or bromine.

X-ray opaque sodium iodide was being injected into veins as a treatment for syphilis. Work undertaken at the Mayo Clinic to determine the fate of the injected sodium iodide pointed to excretion by the kidneys. Leonard Rowntree recognized that an x-ray opaque substance was being removed from the circulating blood and concentrated in the kidneys. This suggested to Rowntree that intravenous injection of sadium iodide might yield a valuable technique for x-ray visualization of the kidneys and the urinary bladder. Using this technique, the Mayo Clinic group of Osborn, Sutherland, Scholl, and Rowntree obtained excellent roentgenograms of the otherwise invisible kidneys and urinary tract.[40] The same L.G. Rowntree who contributed to this 1923 report from the Mayo Clinic had published with John J. Abel (1910) a paper on the pharmacological action of phthaleins which would be crucial to the Graham and Cole experiments.

The four Mayo Clinic authors also noted x-ray opacification of the injected veins in their kidney and urinary bladder experiments and boldly suggested that sodium iodide injection of vessels might be a valuable diagnostic procedure.

> In all probability, with variations in the technic, important results will be obtained with regard to the venous returns and the peripheral arterial circulation.

In fact, the first visualization of an x-ray opaque vessel following the injection of a soluble iodine compound had already been performed by Carlos Heuser of Argentina. In 1919 Heuser reported that he had been able to demonstrate veins and even the chambers of the heart following the intravenous injection of potassium iodide.[41] Rediscovery of this radiologic technique occurred on September 23, 1923 at Barnes Hospital. Barney Brooks, a colleague of Graham and Cole in the Department of Surgery, obtained remarkably clear x-ray films of the arteries in a patient's leg following the intravenous injection of sodium iodide.[42] Graham and Cole were attempting x-ray visualization of the gallbladder when Brooks achieved this success.

Physiology of the Gallbladder and Phthalein Pharmacology

The contrast media used by Graham and Cole was a phthalein, a class of compounds first described by Baeyer in 1871.[43] In 1924 it was common knowledge that a halogenated phthalein is x-ray opaque.[44] In addition, the following research reports were very much on Graham's mind when he began to study halogenated phthaleins with a view toward x-ray visualization of the gallbladder:[45]

1910 The excretion by the liver of several halogenated phenophthaleins into the bile is reported by Abel and Rowntree.[46]

1921 The ability of the normal gallbladder to concentrate bile up to ten times through the removal of water is reported by Rous and McMaster.[47]

Discovery of the Graham-Cole Technique

Before beginning experimental work, Graham and Cole knew that halogenated phenophthaleins were opaque to x-rays, that these compounds

were excreted in the bile, and that the bile was concentrated in the gallbladder. However, the experimenters injected two hundred dogs and rabbits with halogenated phenolphthaleins before obtaining an x-ray visualization of the gallbladder. In November, 1923, good fortune provided the breakthrough. Working with an animal that accidently had not been fed, x-ray films showed opacification of the gallbladder. Only a short time before, E.A. Boyden had demonstrated that a meal will cause the gallbladder to empty[48]--a report with which Cole was familiar.[49] For the first two hundred animal experiments, the animals had been fed after receiving the injection of a halogenated phthalein. Graham and Cole had been taking x-ray films after the gallbladder had emptied its dose of contrast medium. This first successful cholecystogram was easily reproduced in additional fasting animals and later in fasting humans.[29]

By contributing to the reliable diagnosis of gallbladder disease, the Graham-Cole x-ray examination insured the more appropriate use of the cholecystectomy procedure. The Graham-Cole test was rapidly adopted and widely applied. Eighteen months after first reports of this cholecystography technique, Carman announced to the First International Congress of Radiology that,

> During the last 15 months more than 1,100 patients have been examined at the Mayo Clinic by cholecystography. . . . The affirmative diagnoses of disease appear to be well sustained, and there were few disappointments in this series. Negative findings with the dye tend to be somewhat less reliable.[50]

Improving the Graham-Cole Procedure

Before the end of 1925, two modifications of the original Graham-Cole technique were introduced. When iodine was substituted for bromine in the intravenously injected phenophthalein salts, the nausea, vomiting, and prostration which patients commonly suffered were for the most part prevented. Only somewhat later, it was observed that oral instead of intravenous administration of the bromine compound would usually give adequate filling of the gallbladder with the contrast medium.

Since 1925 halogenated compounds which reach greater gallbladder concentrations with fewer side effects have been introduced. In certain situations where the Graham-Cole procedure will not give an adequate x-ray examination, today's radiologist will resort to the more dangerous transabdominal needle puncture of the bile ducts with direct injection of contrast medium. However, the Graham-Cole cholecystogram remains the mainstay of radiologic examination of the gallbladder. The x-ray films of the gallbladder which Evarts Graham and Warren Cole examined late in 1924 had the same detail and clarity as the best results of today's radiologists.

IV. Conclusions.

In the eighty years since Roentgen's discovery of x-rays, radiology has come to be routinely employed for examining most of the internal organs of the body. The skills of a diagnostic radiologist may be called for when gastric ulcers, fractures, pulmonary tuberculosis,

spinal cord trauma, gallstones, or cancer of an internal organ is suspected. With x-ray examination used in the diagnosis and management of scores of diseases, the general diagnostic radiologist may expect daily contact with cases from the medicine, surgery, and pediatrics services. In an age of increasing health care specialization, the diagnostic radiologist has expanded his repertoire of examinations to deal with a broad range of disease entities.

Of the many organs and diseases to which x-ray examination has been adopted, only pulmonary tuberculosis and the biliary tract have been considered in this short history. Improvements in x-ray equipment, skilled interpretation of x-ray films, and introduction of contrast media have enhanced the value of these x-ray studies.

Reliable power sources, the Coolidge tube, and other improvements in equipment have dramatically increased the detail and clarity of x-ray films.

In the case of pulmonary TB, the correlation of x-ray findings with lung pathology and integration of x-ray studies with changing methods of treatment continued to unfold into the 1950's. In comparison to the slow evolution of chest radiology, the introduction of the Graham-Cole cholecystogram was an overnight revolution.

In 1924 surgery of the gallbladder and bile ducts had reached the stage of safe and highly efficacious treatment. However, the diagnosis of biliary tract disease was still unreliable. Introduction of the Graham-Cole cholecystogram (1924) limited costly errors in diagnosis and assured more appropriate utilization of surgical treatment. Today radiology continues to play a key role in detection and management of

biliary tract disease and pulmonary TB.

FOOTNOTES

1. The following histories have been used for this short history of diagnostic radiology:

Ruth and Edward Brecher, 1969, The Rays - A History of Radiology in the United States and Canada, (Baltimore: Williams and Wilkins Co.).

Andre J. Bruwer, 1964, Classic Descriptions in Diagnostic Roentgenology, (Springfield: Charles C. Thomas Co.).

2. Wilhelm Conrad Roentgen, "On a new kind of rays. (Preliminary communication)" Sitzungs-Berichte der Physikalisch-medicinischen Gesellschaft zu Wurzburg, dated December of 1895 but released in early January of 1896.

3. John Cox, Trans. Roy. Soc. Canad., Ser. 2, 2:171-191, 1896.

4. William Osler, 1892, The Principles and Practice of Medicine, (Edinburgh & London: Young J. Pentland), pp. 184-256.

6. Osler, 1892, Principles and Practice of Medicine, p. 230.

5. William W. Stead, 1970, Principles of Internal Medicine, (New York: McGraw-Hill), pp. 865-880.

7. William Osler, 1901, The Principles and Practice of Medicine, (New York: D. Appleton and Co.), p. 328.

8. Osler, 1901, Principles and Practice of Medicine, pp. 258-338.

9. Francis H. Williams, 1901, The Roentgen Rays in Medicine and Surgery, (New York & London: The MacMillan Co.).

10. Williams, 1901, The Roentgen Rays, p. 115.

11. Williams, 1901, The Roentgen Rays, p.117.

12. Williams, 1901, The Roentgen Rays, pp. 124-125.

12. Sir William Osler, 1912, The Principles and Practice of Medicine, (New York & London: D. Appleton and Co.), p. 208.

13. Sherman G. Bonney, 1908, Pulmonary Tuberculosis and Its Complications, (Philadelphia & London: W.B. Saunders Co.), pp. 256-258.

14. Brecher, 1969, The Rays, pp. 55-58.

15. R.B. Wisley, "The Intensity of Scattered X-Rays in Radiography," Amer. J. Roentgen., 8:328-338, 1921.

16. Thomas McCrae, 1930, The Principles and Practice of Medicine, (New York & London: D. Appleton and Co.), p. 210.

17. Thomas McCrae, 1935, The Principles and Practice of Medicine, (New York & London: D. Appleton and Co.), p. 212.

18. Brecher, 1969, The Rays, pp. 209-210.

19. Henry A. Christian, 1938, The Principles and Practice of Medicine, (New York & London: D. Appleton-Century Co.), p. 239.

20. Christian, 1938, Principles and Practice of Medicine, p. 256.

21. Henry A. Christian, 1942, Principles and Practice of Medicine, (New York & London: D. Appleton-Century Co.), p. 259.

22. Christian, 1942, Principles and Practice of Medicine, p. 259.

23. Christian, 1942, Principles and Practice of Medicine, pp. 256-257.

24. Paul C. Hodges and Russell H. Morgan, "Photoelectric Timing in General Roentgenography," *Amer. J. Roentgen.*, 53:474-482, 1945.

25. William Kirby, 1950, *Principles of Internal Medicine*, editor in chief: T.R. Harrison, (New York, Toronto, and Philadelphia: The Blakiston Co.), p. 914; and 1962, *Principles of Internal Medicine*, (New York, Toronto, and London: McGraw-Hill Co.), pp. 1005-1006.

26. Stead, 1970, *Principles of Internal Medicine*, p. 871.

27. Osler, 1892, *Principles and Practice of Medicine*, p. 227.

28. Marcellus Donatus, *De medica historia mirabili libri sex*, trans. by Ralph H. Major, 1932, *Classic Descriptions of Disease*, (Springfield: Charles C. Thomas), p. 603.

29. Evarts A. Graham and Warren H. Cole, "Roentgenologic Examination of the Gallbladder," *J.A.M.A.*, 82:613-614, Feb. 23, 1924.

30. Bruwer, 1964, *Classic Descriptions in Diagnostic Roentgenology*, p. 1132.

31. John Chalmers DaCosta, 1919, *Modern Surgery*, (8th ed.; Philadelphia & London: W.B. Saunders Co.), pp. 1170-1192.

32. Seymour I. Schwartz, 1969, *Principles of Surgery*, (New York: McGraw-Hill Co.), pp. 1077-1111.

33. Herman A. Haubold, 1922, *The Principles and Practice of Surgery*, (New York & London: D. Appleton), pp. 2085-2130.

34. John Chalmers DaCosta, 1931, *Modern Surgery*, (Philadelphia and London: W.B. Saunders Co.), pp. 973-974.

35. Russell D. Carman, William C. MacCarty, and John D. Camp, "Roentgenologic Diagnosis of Cholecystic Disease," *Radiology*, 2:80-89, Feb. of 1924.

36. Russell D. Carman, 1917, *The Roentgen Diagnosis of Disease of the Alimentary Canal*, (Philadelphia & London: W.B. Saunders Co.).

37. Russell D. Carman, "Roentgen observation of the gallbladder and hepatic ducts after perforation into duodenum," *J.A.M.A.*, 65:1812, Nov. 20, 1915.

38. H. Burckhardt and W. Muller, "Versche uber die Punktion der Gallenblase und ihre Rontgendarstellung," *Deutsche Zeitschr. f. Chir.*, 162:168-197, reproduced in English translation in Bruwer, 1964, *Classic Descriptions in Diagnostic Roentgenology*.

39. Brecher, 1969, *The Rays*, p. 235.

40. Earl D. Osborne, *et al.*, "Roentgenography of Urinary Tract During Excretion of Sodium Iodid," *J.A.M.A.*, 80:368-373, Feb. 10, 1923.

41. Carlos Heuser, *La Semana Medica* (Buenos Aires), 26:424, 1919.

42. Barney Brooks, "Intra-Arterial Injections of Sodium Iodid," *J.A.M.A.*, 82:1016-1019, March 29, 1924.

43. Adolf Baeyer, "Ueber die Phenolfabstoffe," *Ber. Dtsch. Chem. Ges.*, 4:658-665, 1871.

44. Ernst Sehrwald, "Das Verhalten der Halogene gegen Röntgenstrahlen," *Deutsch. Med. Wschr.*, 30:477-480, July 23, 1896.

45. Warren H. Cole, "The Story of Cholecystography," *Am. J. Surg.*, 99:206-222, Feb. 1960; and "Historical Features of Cholecystography," *Radiology*, 76:354-375.

46. John J. Able and L.G. Rowntree, "On the pharmacologic action of some phthaleins and their derivatives," J. Pharmacol. & Exper. Therapy, 1:231-264, 1910

47. P. Rous and P.D. McMaster, "The Concentrating Activity of the Gallbladder," J. Exper. Med., 34:47-73, July of 1921.

48. E.A. Boyden, "The gallbladder in the cat," Anat. Rec., 24:388, 1922-1923.

49. Cole, Am. J. Surg., 99:206-222.

50. Russell D. Carman, "Cholecystography in its Application to the Diagnosis of Cholecystic Disease," Lancet, 2:67-69, July 11, 1925.