

Primary carcinoma of the veriform appendix : a critical study of 90 cases, with references to 123 cases / by Clarence A. McWilliams.

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VII.

PRIMARY CARCINOMA OF THE VERMIFORM
APPENDIX.

A CRITICAL STUDY OF 90 CASES, WITH REFERENCES TO 123 CASES.*

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The increasing reports of isolated cases of primary carcinoma of the appendix, which one finds in the literature, testify not only to the greater interest now manifested in the study of the pathological anatomy of that organ, but also to the greater care exercised in its examination, whether removed at operation or on the autopsy table. A sufficient number of such neoplasms has now been recorded to make a critical study of them interesting and instructive. To the 87 cases that I have found reported in the literature, I desire to add the following 3 cases:

Case XXII.—An unmarried, German, immigrant girl, aged twenty years, was admitted, on September 5th, 1907, directly from the steamer to the Presbyterian Hospital, to the service of Dr. F. T. Brown, to whom I am indebted for the privilege of taking care of and reporting the case. Except for some seasickness, she had been well up to two days prior to landing, at which time she was taken with severe pain in the right side of the abdomen. She had fever, and was markedly prostrated. The right lower quadrant of the abdomen became very tender to pressure. On admission to the Hospital, her temperature was 101°, and her pulse

*The reports of 33 additional cases were found after the statistics in this article had been completed. Since it was impossible to include them in the detailed study, they have been added in an appendix. The total number of cases reported, therefore, is 123. The literature is brought down to Jan. 1, 1909.

100. The leucocytes were 23,000, and the polymorphonuclears, 88 per cent. She had never been sick before, and there was no history of any pelvic disturbances. While evincing evidences of considerable prostration, at the same time she was very well nourished, and there was no sign of any cachexia. Physical examination showed the heart and lungs to be normal. The abdomen was distended and there were no respiratory abdominal movements. The whole right lower quadrant was rigid and very tender, both these signs shading off from a point of maximum intensity, situated at McBurney's point, where there was felt a mass the size of a lemon. Over this mass there was tympany, and there were no signs of free fluid in the abdomen. Rectal examination showed the pelvic organs to be normal, and no mass could be felt, but there was considerable tenderness high up in the right fornix.

Immediate operation was performed. An intermuscular incision, about two inches long, was made over the mass. On opening the peritoneum, the inserted finger pushed aside an adherent coil of intestine, which opened an abscess, well walled in, containing about two ounces of fetid, thick, creamy pus. After sponging the cavity dry, the appendix was found hanging over the brim of the pelvis, to whose walls it was adherent. On delivering it into the wound, it was seen to be about four inches long and as large as one's index finger. Its serosa was intensely congested, and about one inch from its base there was a gangrenous patch, in the centre of which there was a small perforation. Its tip was clubbed and hard, as though there was a concretion in its lumen. The meso-appendix was clamped in sections and divided. Two catgut ligatures were applied about its base, between which the appendix was amputated. The stump was cauterized by the Paquelin, after which a second plain catgut ligature was applied about the stump, which was followed by a second cauterization. The cavity was sponged out, and into it were inserted two small cigarette drains. The abdominal wall was sutured by layers, closely about the drains. The patient made an unevent-

ful recovery, the wound being completely closed by the twenty-fifth day. The girl went home on the thirtieth day.

At the time of the operation there was no suspicion that the appendix, on external examination, was affected with anything more than an intense, acute suppurative inflammation. Owing to the lateness of the hour in the evening of the operation, the appendix was not cut open, but, following the ordinary routine, it was sent, as it was removed, to the pathologist, by whom a gross section of the organ was made, and this revealed, macroscopically, that the tip, for half an inch, was occupied by a small fibrous appearing mass, which completely filled the lumen. There was no concretion present. No suspicion of malignancy whatsoever was aroused at the time of the operation, as there was no tumor visible on the external surface, the tip being merely clubbed. No enlarged glands were seen in the meso-appendix.

The following is the report of the examination of the specimen by Dr. F. C. Wood, of the Pathological Department of Columbia University: The material consists of four transverse sections of the appendix. Two of the fragments include a considerable portion of the meso-appendix. The other two are transverse sections of the free part of the organ. The appendix is considerably enlarged, measuring about 12 mm. in diameter after hardening. Two of the sections show merely a dilated appendix with no mucosa and a somewhat chronically inflamed peritoneum and subserous coats, the wall measuring 4 mm. in thickness. The other two specimens, which include the meso-appendix, show the following changes: The wall is thickened, measuring 6 mm. This thickening is chiefly in the submucosa and muscularis. At the periphery of the appendix and in the meso-appendix are a large number of leucocytes and blood. The leucocytes are chiefly polynuclear, many of them of the eosinophile group. The rest are lymphocytes and plasma cells. The fat of the meso-appendix is infiltrated, and there is a formation of a considerable amount of new connective tissue in the form of granulation tissue.

The blood vessels are distended with blood. There is a thrombus in one of the larger veins. This more or less active inflammation extends entirely around the appendix, although in the portion opposite the mesenteric attachment the inflammation is much less than on the other side. The mucous membrane of this portion of the appendix is normal and the surface is unbroken. The submucosa, the muscularis, and the subserosa are infiltrated with cells arranged in large and small masses in the tissue spaces (Figs. 1, 2, and 3). These cells are polyhedral (Figs. 4 and 5); there is no connective tissue between the individual cells; the nuclei are large and show well arranged chromatin network. Mitotic figures are scanty. None of the carcinomatous masses show any tendency to an alveolar formation, nor are there any high cylindrical or mucous cells. While the new growth extends up into the lymphoid tissue underneath the lining membrane of the lumen of the appendix, this epithelium is in no place broken through, nor in direct connection with the growth. The infiltrated tissue shows the usual evidence of chronic inflammation, and many wandering tissue cells of the type of plasmacytes and plasma cells are present in the muscle bundles near the new growth. The exact histogenesis of the tumor cannot be established from the specimen, as the entire appendix is not available for section; but the possibility of the tumor having arisen from the mucous membrane cannot be excluded. The diagnosis is carcinoma of the appendix, polyhedral cell type; acute peri-appendicitis.

Case XXVI.—Operator, Dr. J. Wiener. A male, aged thirty-five years, was admitted to Mt. Sinai Hospital, New York, December 8th, 1903. As a child, inflammation of bowels. Five years ago, indigestion for six months with nausea and belching of gas, appetite fair, but with no pain. One year ago, nervous prostration, which kept him from work for six months. Moderate smoker, but not alcoholic. Eleven days before admission, sudden sharp, shooting pains in right lower quadrant. Next morning

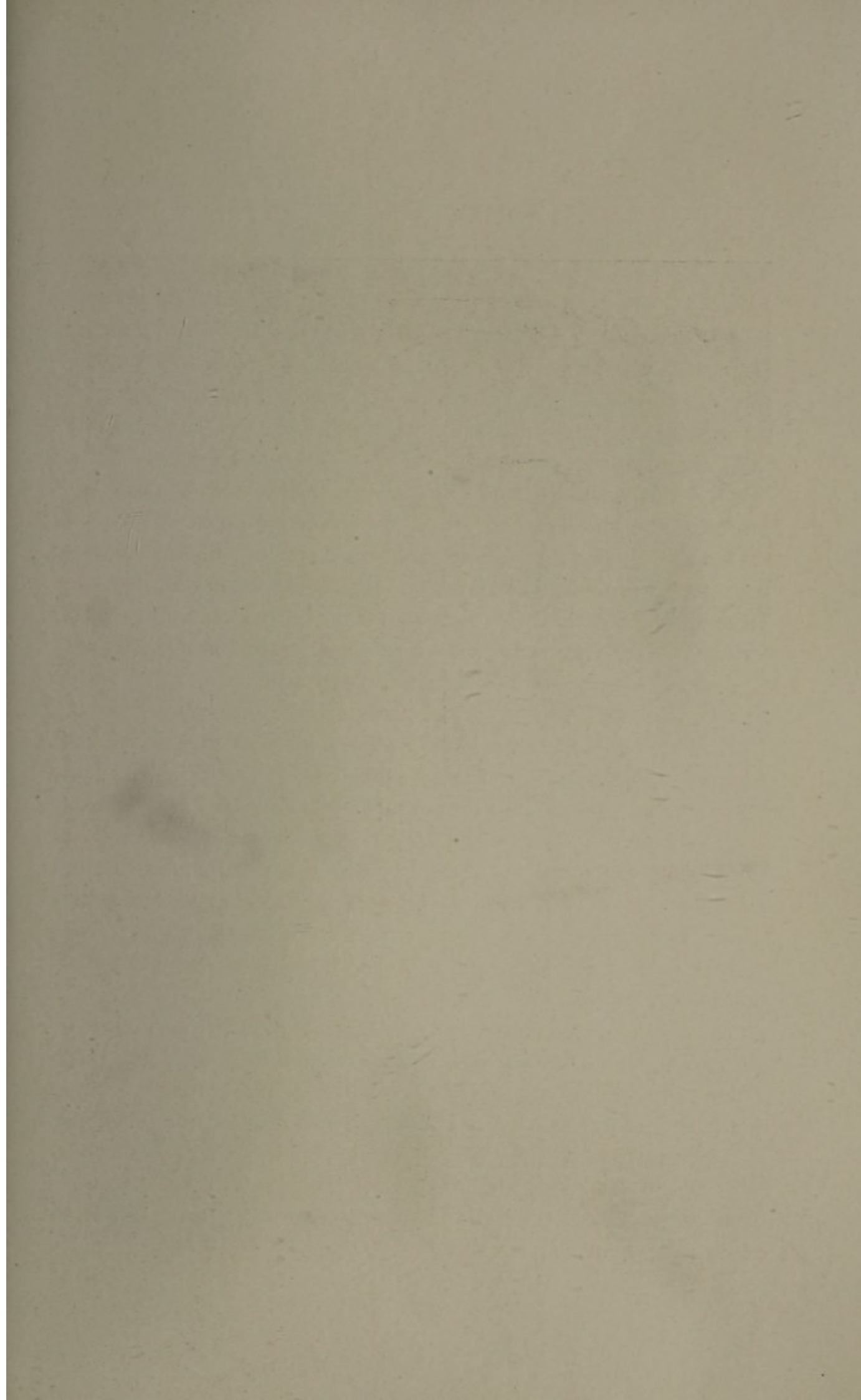




FIG. 1—CARCINOMA OF THE APPENDIX (CASE XXII)
SHOWING GENERAL DISTRIBUTION OF THE GROWTH THROUGHOUT THE WALL OF THE ORGAN. (LOW POWER.)



FIG. 2—CARCINOMA OF THE APPENDIX (CASE XXII)
SHOWING GENERAL DISTRIBUTION OF TUMOR THROUGHOUT THE WALL OF THE APPENDIX. (MEDIUM POWER.)

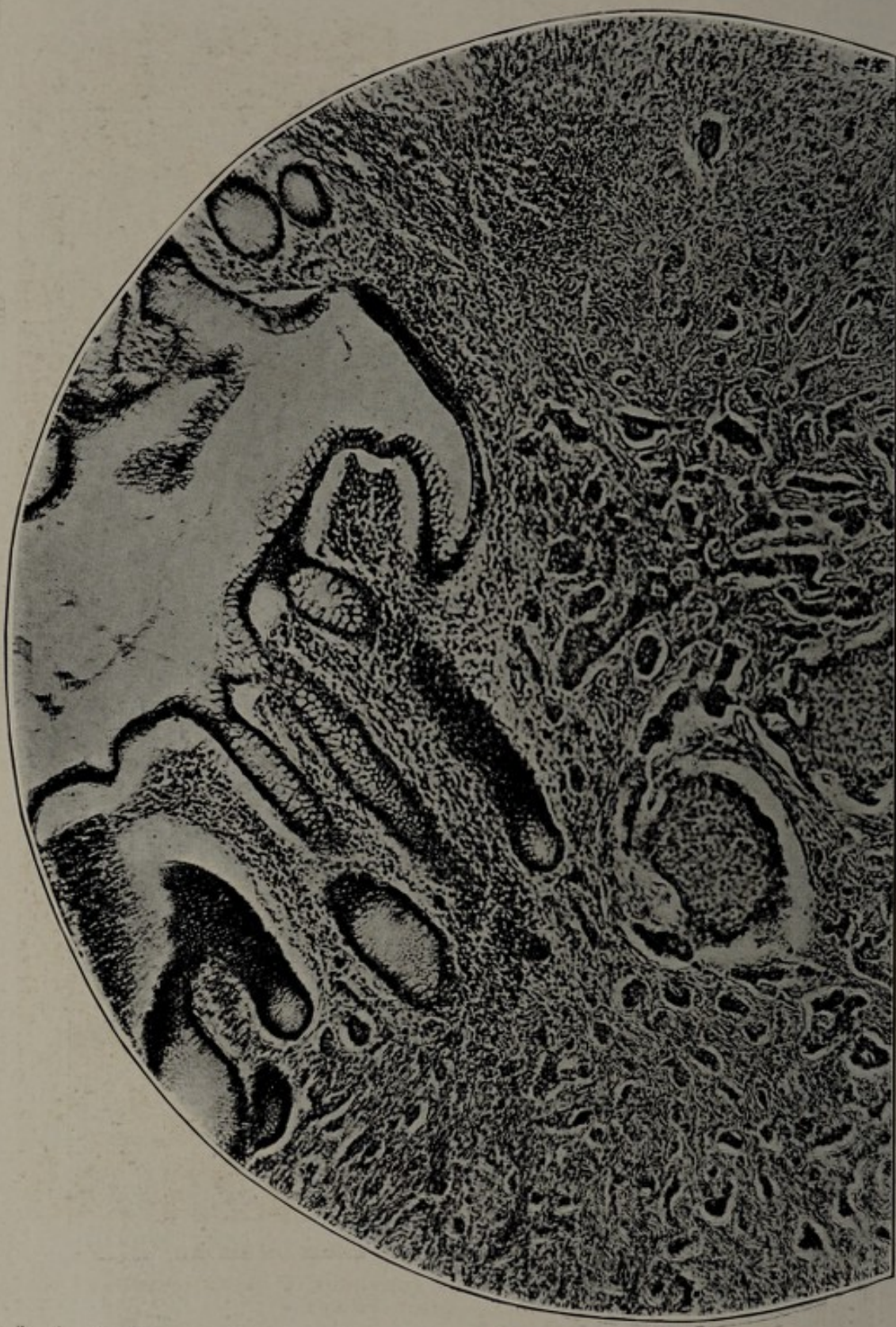


FIG. 3—CARCINOMA OF THE APPENDIX (CASE XXII)
SHOWING THE TOPOGRAPHY OF THE GROWTH BENEATH THE MUCOSA. (MEDIUM POWER.)



FIG. 4.—CARCINOMA OF THE APPENDIX (CASE XXII)
SHOWING SOLID ALVEOLI FILLED WITH POLYHEDRAL CELLS INVADING THE
SUBMUCOSA. (HIGH POWER.)

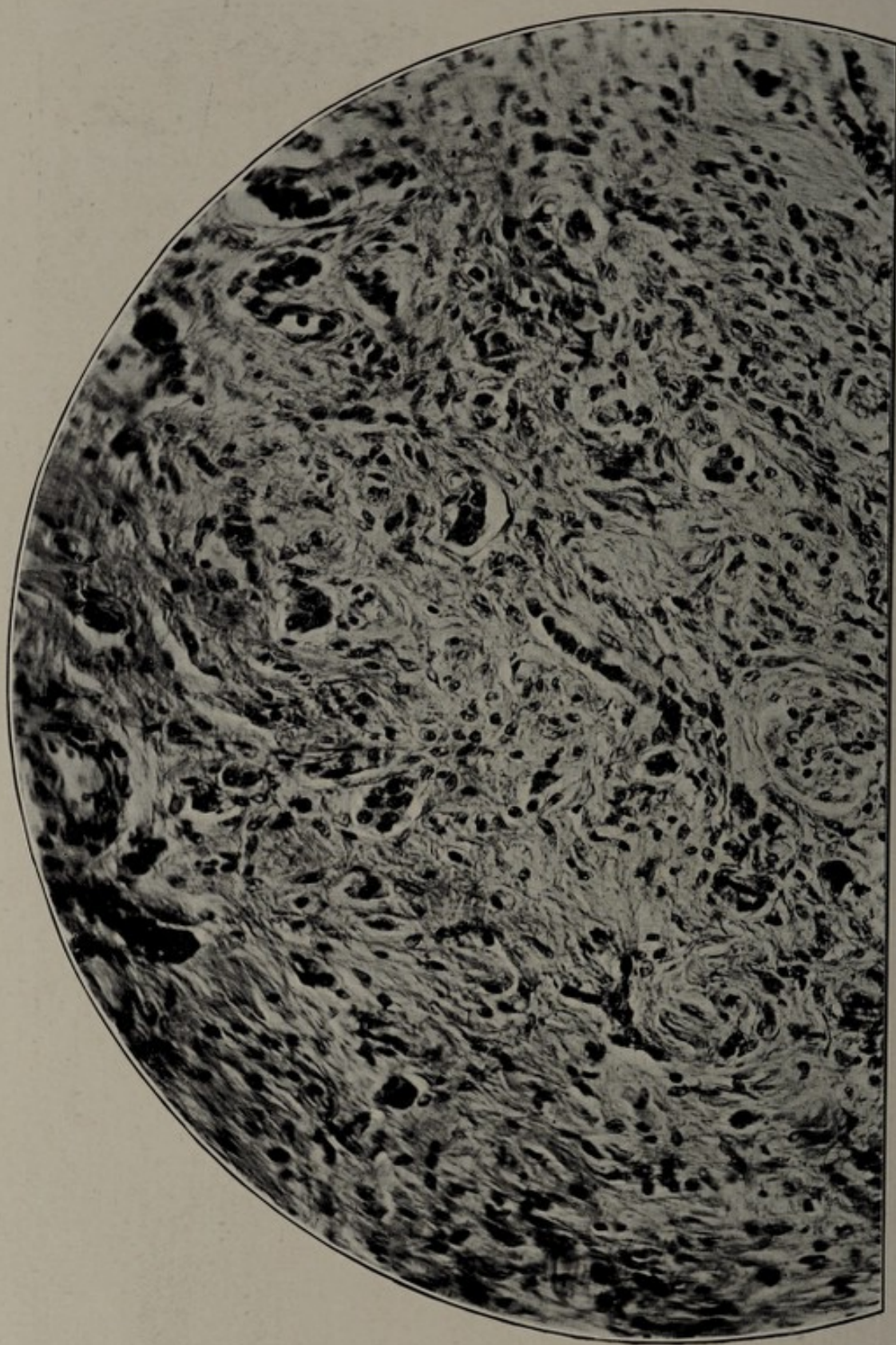


FIG. 5—CARCINOMA OF THE APPENDIX (CASE XXII)
SHOWING SOLID ALVEOLI FILLED WITH POLYHEDRAL CELLS (HIGH POWER)

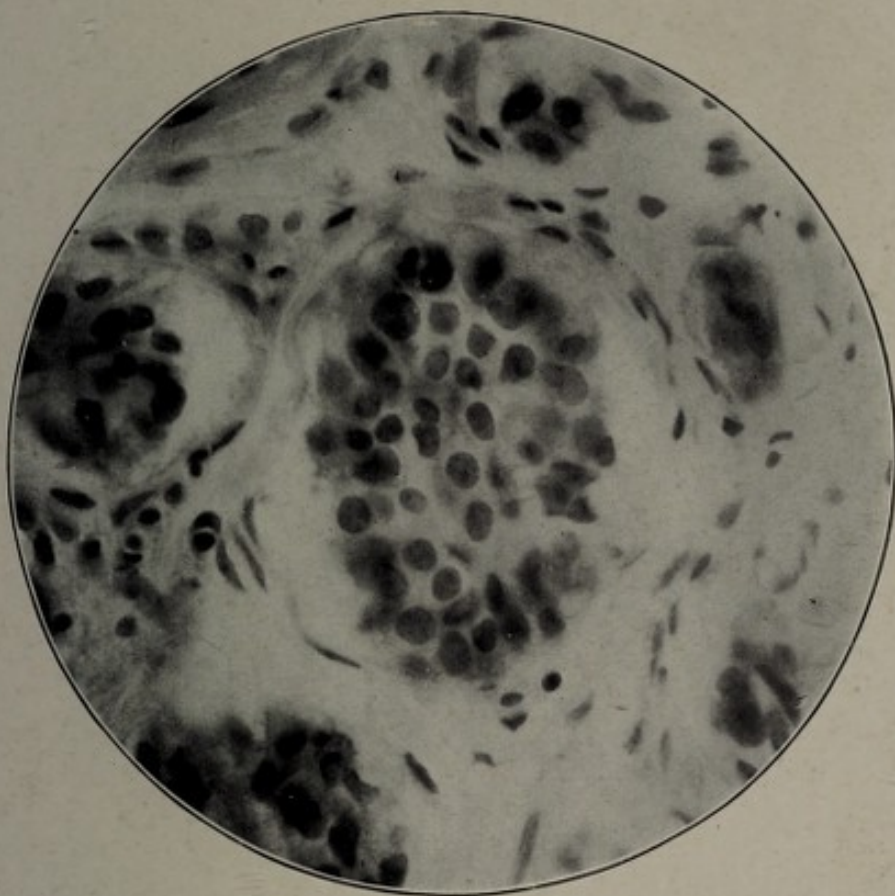
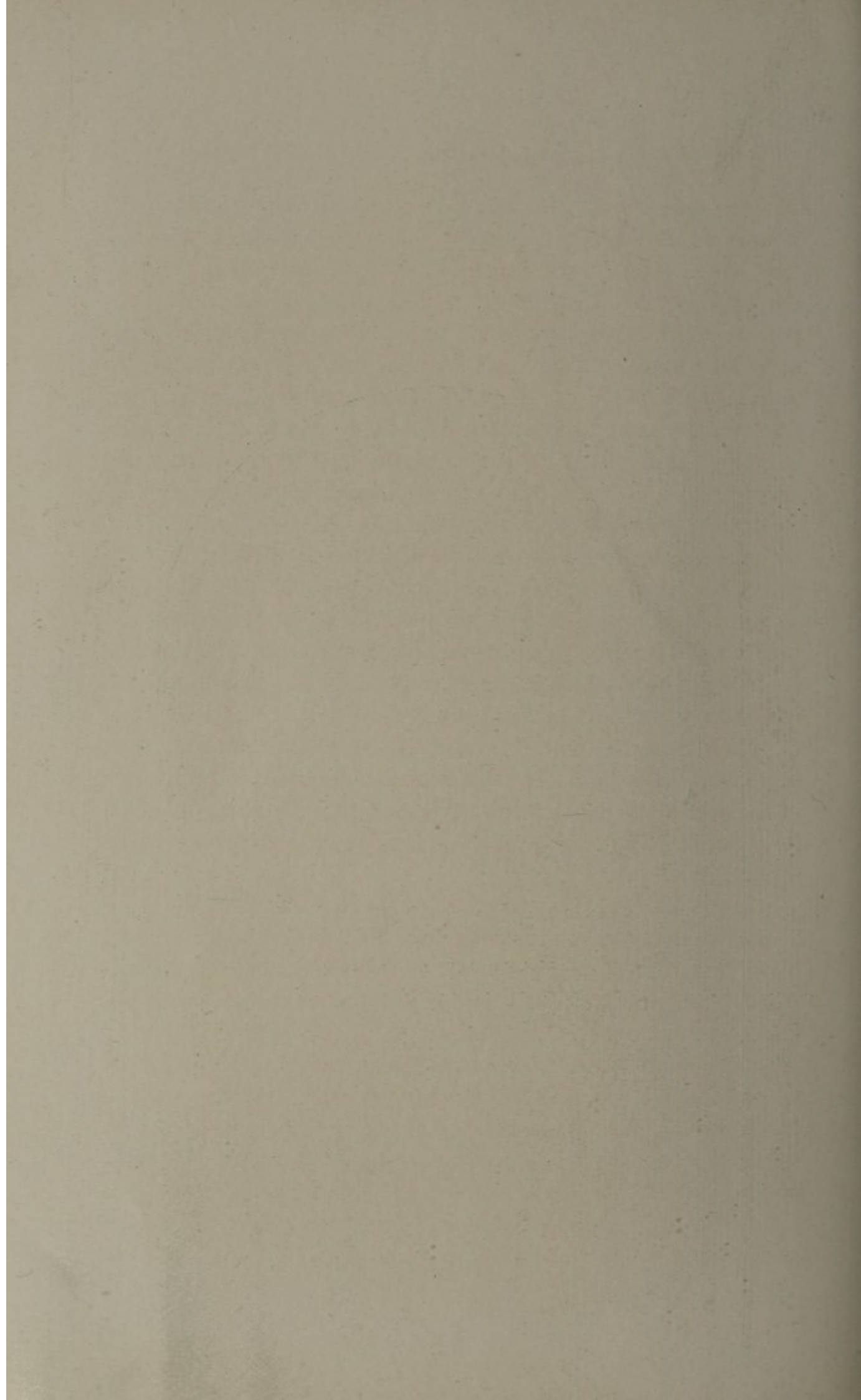


FIG. 6—SPHEROIDAL-CELL CARCINOMA OF THE APPENDIX (CASE XXVII)

SCATTERED IRREGULARLY BETWEEN THE MUSCLE BUNDLES ARE ALVEOLI FILLED WITH IRREGULAR OVOID OR POLYHEDRAL CELLS WITH LARGE NUCLEI. IN OTHER PORTIONS THERE IS A DIFFUSE INFILTRATION OF THE MUSCLE TISSUE WITH SIMILAR CELLS. THERE ARE NO MITOSES VISIBLE IN THE CELLS. DIAGNOSIS: SPHEROIDAL CELLED CARCINOMA OF THE APPENDIX.



went to business, but about 11 A. M. felt nauseated, with chilly sensations and profuse sweating. Severe umbilical pains. A few hours later, temperature 103.6° . No vomiting. Bowels moved spontaneously. Went to bed and had fever and chilly sensations for three days, when the pain became localized in the right iliac fossa. Operation December 9th, 1903, at which time nothing palpable in the right iliac fossa was felt, but there was slight tenderness on deep pressure in that region. Intermuscular incision. Many dense adhesions between cecum, parietal peritoneum, and ileum. Appendix firmly adherent below and internally to cecum. Separation of adhesions caused tearing of serosa of cecum in several places, which were repaired with silk sutures. Appendix two inches long, very narrow, especially at base; near its tip, and projecting into the meso-appendix, was what was taken to be a small gland. In the mesentery, near the ileocecal junction, a large gland was found and removed. This gland, together with the tip of the appendix, was submitted to the pathologist, Dr. Mandlebaum. Out of bed on the tenth day, and the wound healed in two weeks. The diagnosis is adenocarcinoma near tip of the appendix; obliterating appendicitis; hyperplasia of mesenteric gland. The patient was well four years later, that is, at the present time.

Case XXVII.—Operator, Dr. A. J. McCosh. A male, aged twenty-five years, was admitted to the Presbyterian Hospital, New York, April 7th, 1897. His difficulty began in the previous August, when he had sudden cramp-like pains in the right lower abdomen, accompanied by vomiting. No abdominal tenderness (?). The pains lasted two weeks. The next month, September, he had a similar attack, lasting three weeks. He was well until the following March (an interval of six months), when he was taken with sudden tenderness and pains in the right iliac fossa, abdominal distention, and vomiting. On admission, he was just recovering from this last attack. On examination, there were rigidity and tenderness in the right iliac fossa. At the operation

there was no fluid in the abdomen. There was felt a mass, three and one-half inches in diameter and one and one-half inches deep, with no pulsation in it. It was gradually mapped out, running obliquely behind the posterior peritoneum from the sacrum up to the right side. The appendix was not seen. An aspirating needle introduced into the boggy tumor withdrew no pus. It was deemed a malignant mass, involving the cecum, appendix, and peritoneum. Removal was considered impossible, and the wound was closed. The patient was readmitted January 4th, 1899, twenty months after his first operation. For the past eight months he has had attacks of cramp-like pains in the region of the old scar, and these attacks are now recurring much more frequently. Has lost no flesh or strength; never jaundiced, and bowels regular. On examination, in old appendix wound, there is a small ventral hernia. Palpating through this opening, there is found, at the usual site of the appendix, a hard mass, size of a walnut. Operation, January 10th, 1899. Intestines and omentum matted together and covered with a serous exudate. Several large, hard masses felt in the posterior part of the abdomen, which proved to be retroperitoneal glands. The glands throughout the mesentery were enlarged and hard. Several of these were excised for examination. The appendix was separated from adherent intestines with much difficulty. It was short, thick, and gave evidences of chronic inflammation. The fluid from this region had a foul odor. Appendix removed. Incision closed with drainage.

Pathological number, 4239. Dr. Thacher. October 1st, 1899. Appendix and glands. In some parts of some sections there is a cancerous structure. Some alveoli are round and have a lumen, others are round and packed with cells, others are long and narrow, in places only a single row of cells. Some of the alveoli lie in smooth muscle. There is inflammatory exudation at the surface of some portions. The lymph glands look normal. After-history: This patient was seen in March, 1908, and was in perfect health.

There is a symptomless ventral hernia in the scar, but nothing abnormal is palpable in the iliac fossa. There has been, consequently, no recurrence after nine years.

Fortunately the slides were preserved. I submitted them to Dr. Wood, of Columbia University, on February 20th, 1908, for the purpose of obtaining a photomicrograph, which is here reproduced (Fig. 6). His pathological report is as follows: The specimen consists of three mounted sections of a portion of the intestinal tract. From the thickness of the wall and the fact that there are four or five small gland tubules embedded in the lymphoid tissue, in one portion of one section, it is probable that the material was removed from the appendix. The muscular coats are arranged in a circular and longitudinal group, and scattered irregularly between the muscle bundles are alveoli, filled with irregularly ovoid or polyhedral cells, with large nuclei containing well-marked chromatin. In other portions there is a diffuse infiltration of the muscle tissue with similar cells. At no place has the growth assumed an alveolar type. There are no mitoses visible in the cells. There is only very slight inflammatory reaction around the alveoli containing the cells of the newgrowth. There is no evidence of chronic inflammation of other portions of the tissue. The diagnosis is spheroidal-celled carcinoma of the appendix; whether primary in the appendix or not, it is impossible to say from the sections.*

In connection with these cases, I have gone over the literature and have collected all the reported cases of primary carcinoma of the appendix that I could find after exhaustive search. In 1906, Rolleston and Jones published a report of forty-two cases of malignant tumors primary in the appendix, all doubtful cases having been excluded. Since Rolleston's paper, no collection of such cases has appeared in English. I have found forty-eight cases in all, which in addition to those of Rolleston, make

* That it was primary in the appendix is proved by the material removed at the operation and by the non-recurrence after nine years.

a total of ninety undoubted cases. No case in which the tumor has been found involving the cecum, even to the slightest degree, has been included in either series, because, in such cases, it is impossible to say where the cancer originated, whether in the cecum or in the appendix.

The following is a list of forty-eight cases. The number before each case refers to the corresponding references throughout this article:

- I. Landau. Berl. klin. Woch., December 10, 1906.
- II. Villar. Gaz. hebdom. des Soc. méd. de Bordeaux, January 3, 1904, p. 3.
- III. Weinberg. Bull. et mém. de la Soc. anat. de Paris, 1905, No. 3, p. 38.
- IV. Baldauf. Albany Medical Annals, December, 1905.
- V. Baldauf. Ibid.
- VI. Baldauf. Ibid.
- VII. Warthin. Physician and Surgeon, Detroit, December, 1906, p. 544.
- VIII. Eccles. Amer. Jour. Med. Sci., June, 1906, p. 966.
- IX. Fauldner. Lancet, 1906, i, 598.
- X. Brandts. Munch. med. Woch., 1907, September 3, p. 1780.
- XI. Brandts. Ibid.
- XII. Dreissen. Beiträge zur klin. Chir., 1907, liv, 252.
- XIII. Lejars. Bull. et mém. de la Soc. de Chir. de Paris, March 12, 1907.
- XIV. Zaaier. Beiträge zur klin. Chir., liv, 308 (No. 1 of his cases).
- XV. Zaaier. Ibid. (No. 2 of his cases).
- XVI. Zaaier. Ibid. (No. 3 of his cases).
- XVII. Zaaier. Ibid. (No. 4 of his cases).
- XVIII. Kaufmann. Spec. patholog. Anat., 1904, 3d edition, p. 464. Case 1.
- XIX. Kaufmann. Ibid. Case 2.
- XX. Jong. Mitt. aus d. Grenzg. der Med. und Chir., 1907, xviii, Nr. 3.
- XXI. Hessberg. Carcinoma Processus Vermiformis, Inaug. Diss., München, 1904.
- XXII. McWilliams. This article, p. 1.
- XXIII. Zaaier. Same reference as Cases 14, 15, 16, 17 (his Case No. 5).
- XXIV. Zaaier. Ibid. (his Case No. 6).
- XXV. Zaaier. Ibid. (his Case No. 7).
- XXVI. Wiener. This article. Not previously published, p. 8.
- XXVII. McCosh. Ibid., p. 4.
- XXVIII. Barrow. Georgia Practician, February 15, 1905.
- XXIX. Pauchet. Gazette médicale de Picardie, 1900, xviii, 146.
- XXX. Nélaton. Bull. et mém. de Soc. de Chir. de Paris, March 12, 1907, p. 228.
- XXXI. Hartmann. Ibid., March 5, 1907, Case 1.
- XXXII. Hartmann. Ibid., Case 2.

- XXXIII. Mason and Rhea. *Boston Med. and Surg. Jour.*, January 10, 1907. p. 44.
- XXXIV. Grunbaum. *Berl. klin. Woch.*, August 5, 1907, Nr. 31, p. 984.
- XXXV. Patel. *Lyon médical*, 1907, cix, 276.
- XXXVI. Cullingworth and Corner. *Lancet*, 1904, ii, 1340.
- XXXVII. Neri. *Beiträge zur path. Anat.*, 1905, xxxvii, 163.
- XXXVIII. de Bovis. *Revue de Chir.*, 1900, p. 708.
- XXXIX. Deaver. *Amer. Jour. Med. Sci.*, 1906, p. 845.
- XL. Deaver. *Ibid.*
- XLI. Becker. *Münch. med. Woch.*, July 10, 1906, Nr. 28, p. 1383.
- XLII. Grieg. *Lancet*, 1907, ii, 1466.
- XLIII. Mandlebaum. *Proc. New York Path. Soc.*, 1905.
- XLIV. Mandlebaum. *Ibid.*
- XLV. Korte. *Verhand. der Deut. Gesell. f. Chir.*, 1905, xxxiv.
- XLVI. Korte. *Ibid.*
- XLVII. Korte. *Ibid.*
- XLVIII. Libmann. *Proc. New York Path. Soc.*, 1906, No. 6.

I have excluded the following cases because they have either not seemed to be positively cancerous appendices or else not undoubtedly primary in the appendix:

- De Ruyter. *Archiv. f. klin. Chir.*, Band lxix, p. 281.
- Edington. *Glasgow Med. Jour.*, 1, 120.
- Meyerstein. *Carcinoma Append. Vermiformis*, Inaug. Diss., München, 1905.
- Martin. *Trans. South. Med. and Surg. Assoc.*, xvii.
- Westerman. *Beiträge zur klin. Chir.*, 1907, liv, 258.
- Sudsuki. Three cases of "lymphangitis plastica," *Mitt. aus den Grenzg. der Med. und Chir.* 1901, vii, 516.

The results of the study of these 48 cases are given in the following pages. In many instances they will be found combined with the statistics of Rolleston, in order that certain facts may be more authoritatively established. In no region of the body are we able to obtain cancers in such an early stage of their development as those occurring primarily in the vermiform appendix, and their careful study should in future elicit new and important information with regard to many points in the life history of malignant neoplasms. Consequently, every case should be accurately observed and reported. Now that attention has been drawn to its occurrence so frequently, it can no longer be considered a curiosity.

REASONS WHICH LED TO THE REMOVAL OF THE APPENDIX.—Of the 48 cases in this series, details are wanting as to this point in 3. Of the 45 remaining cases, 2 appendices were removed at autopsies for other conditions, namely, Case XVIII (Kaufmann), in which the distally enlarged appendix was removed from the body of a woman, aged thirty-one years, who had died in the fourth week of typhoid; and second, Case XXI (Hessberg), in which the primary cancer was found in the appendix of a woman, aged seventy-six years, who had died of general miliary tuberculosis and arteriosclerosis; 36 of the remaining 43 patients suffered from some variety of appendicitis. In Rolleston's series of 33 patients who were operated upon, 27 had symptoms pointing to appendicitis in some form. Thus, out of a total of 76 patients operated upon, 63 (83 per cent.) had had such symptoms. Following the latter's classification, I shall divide these as follows:

1. Symptoms of the first acute attack, operation during or immediately after the first acute attack:
 McWilliams, 13 (Cases 4, 6, 22, 24, 26, 29, 30, 31, 34, 45, 47, 48, 49).
 Rolleston, 10

 Total, 23, or 36.5 per cent.
2. Chronic symptoms without acute attack:
 McWilliams, 8 (Cases 15, 16, 17, 19, 20, 36, 37, 42).
 Rolleston, 5

 Total, 13
3. Chronic with one or more acute attack:
 McWilliams, 2 (Cases 14, 25).
 Rolleston, 3

 Total, 5
4. Recurrent attacks:
 McWilliams:
 Two attacks, 5 (Cases 3, 10, 13, 23, 28).
 Three attacks, 5 (Cases 5, 8, 9, 12, 44).
 Five attacks, 3 (Cases 2, 27, 32).

 Total, 13
 Rolleston, 9

 Total, 22

From these figures we find that of the 63 patients with some variety of appendicitis, 23 (36.5 per cent.) had their appendices removed during or immediately after the first acute attack. In these cases it would seem more than likely that the growth was the cause of the acute inflammations, acting in a manner similar to a concretion. For the growth may occlude the lumen, causing stagnation of material beyond the tumor with the resulting changes in the mucous membrane, allowing the entrance of micro-organisms, or the same condition may be brought about by ulceration of the surface of the tumor, or its breaking down through lack of nutrition, due to obliteration or compression of the blood vessels. The question then immediately comes up, what causes the growth itself? This will be discussed later.

Forty patients, or 63.5 per cent., had had symptoms of chronic appendicitis in some form for varying periods of time. Of these, 17 are to be found in Rolleston's series, and 23 in my own. I have been able from the imperfect records to ascertain the duration of the symptoms in the following cases:

12 years,	2 cases,	Jones and Simmons, Zaaier.
7 "	2 "	Weinberg, Kelly and Hurdon.
5 "	1 "	Neri.
4 "	2 "	Hartmann, Jong.
3 "	4 "	Moschkowitz, Driessen, Zaaier, Villar.
2 "	5 "	Weir, Burnham, Kaufmann, Zaaier, Mandlebaum, McCosh.
1 "	4 "	Battle, Barrow, Deaver, Eccles.
Many yrs.,	1 "	Kaufmann.
9 months,	1 "	Landau.
7 "	1 "	Baldauf.
3 "	2 "	Lejars, Zaaier.
2 "	1 "	Cullingworth and Corner.
<hr/>		
26 cases.		

These figures show that symptoms existed for over a year in 21 patients (more than 28 per cent.). This lends weight to the theory that chronic inflammatory changes are the cause of malignancy.

It would be interesting to inquire, then, in this connection, how many of these appendices, removed from patients with chronic symptoms associated with cancer, showed the microscopical lesions of chronic inflammation? There were 23 patients in my series with chronic symptoms, and associated chronic lesions were found by the microscope in the following cases: Baldauf (V), Eccles (VII), Brandts (X), Driessen (XII), Zaaier (XIV), Zaaier (XV), Zaaier (XVII), Zaaier (XXV), Deaver (XXXIX), Hartmann (XXXII), Neri (XXXVII), Barrow (XXVIII), Weinberg (III), Mandlebaum (XLIV), Hessberg (XXI), Zaaier (XXIII), McCosh (XXVII).

Thus, out of 23 cancerous appendices removed for chronic symptoms, in 16 (70 per cent.) it is definitely stated that chronic inflammatory lesions were present in addition to the cancers. In the remaining 7 of the 23 cases, the descriptions of the microscopic findings were either too meagre or too indefinite to judge as to this point.

Are we able to find with the microscope chronic lesions in the cancerous appendices removed from patients in the first acute attack? In my own series of 13 acute cases, I found with regard to this question the following to be the facts:

Case	IV. Baldauf.	Chronic lesions were stated to be present.			
"	VI. Baldauf.	"	"	"	"
"	XXII. McWilliams.	"	"	"	"
"	XXIV. Zaaier.	"	"	"	"
"	XXIX. Pauchet.	Not mentioned in record.			
"	XXXI. Hartmann.	"	"	"	
"	XXXIV. Grunbaum.	"	"	"	
"	XLVII. Korte.	"	"	"	
"	XLVIII. Korte.	"	"	"	
"	XLIX. Libman.	Chronic lesions present.			
"	XLV. Mandlebaum.	"	"	"	
"	XXX. Nelaton.	"	"	"	
"	XXVI. Wiener.	"	"	"	

Of these 13 cases, in which cancers were found in appendices removed in the first acute attack, there are 8 (61 per cent.) in

which mention is made of chronic inflammatory lesions being found in addition to the cancers.

In 7 of the 48 cases, the primary cancerous appendix was removed in the course of other operations:

CASE I. Landau. Myomectomy; left salpingoöphorectomy; appendix removed because of bulbous tip. Chronic lesions also present. Female, aged thirty-three years.

CASE VII. Warthin. Acute pelvic abscess, due to pyosalpinx; right salpingoöphorectomy; appendix removed because irregularly thickened. Chronic lesions found with the microscope. Female, aged thirty-two years.

CASE XI. Brandts. Symptoms before operation thought to be due to biliary calculi, because of jaundice and recurring pains. Cholecystectomy. Appendix clubbed. Chronic lesions present in appendix. The author says that the "attacks were due to chronic appendicitis caused by the cancer." Male, aged thirty-five years.

CASE XX. Jong. Patient had diarrhoeal attacks for four years, which were referred to a chronic appendicitis. Removal of the appendix cured the attacks. Appendix found to have a very thick proximal mucous membrane and a stenosis, 2.5 cm. from the tip, which caused a cyst in tip with thick walls. In the appendix, chronic lesions found generally and a cancer in the cyst. Female, aged forty-seven years.

CASE XXXIII. Mason and Rhea. In 1903, cyst of ovary removed. In 1905, resection of the tube and ovary for cyst and hydrosalpinx. In 1906, operation for subacute pelvic pains, curettage, ventrosuspension, resection of ovary, and removal of normally appearing appendix, "to prevent any possible further trouble." Chronic lesions present, as well as a small cancer in the tip, only visible by means of the microscope. Female, aged twenty years.

CASE XXXV. Patel. Operation for double inguinal herniæ. The right one was tender and irreducible, and contained an ad-

herent appendix. No mention in the record of any lesion except the cancer. Male, aged fifty-eight years.

CASE XXXVI. Cullingworth and Corner. Fibromyoma of uterus removed. Appendix amputated because of bulbous tip. Chronic lesions also present. Female, aged thirty-one years.

In these 7 cases, the cancerous appendices were chance findings. The average age of these patients was 36.5 years. Rolleston gives 4 such patients, all operated upon for pelvic lesions.

Summarizing, then, the presence or absence of chronic lesions in my series of 48 cases, I find the following to be the facts:

Among the 23 patients operated upon for chronic appendicitis, 16 were stated to have chronic lesions present, as found by the microscope. Of the 13 patients operated upon for acute appendicitis, 8 were definitely stated also to have chronic lesions present. In 6 of the 7 patients from whom the appendices were removed in the course of other operations, chronic lesions were found. Thus, there was a total of 30 patients out of 48, or 62 per cent., in whose cancerous appendices associated chronic lesions were found by the microscope. Which is primary, the chronic inflammation or the cancer? As yet, there is no correct answer to this question apparently. We may summarize, then, the reasons for the discoveries of the cancers as follows:

	McWilliams.	Rolleston.	Totals.
Acute appendicitis.....	13	10	23
Chronic appendicitis.....	23	17	40
Appendices removed in the course of pelvic operations	4	4	8
Iliac fistulæ.....	0	2	2
Inguinal hernia.....	1 (Case 35)	0	1
Appendectomy and cholecystectomy.....	1 (Case 11)	0	1
Appendectomy for chronic diarrhœa.....	1 (Case 20)	0	1
Autopsies.....	2	8	10
Unknown.....	3	1	4
Totals.....	48	42	90

FREQUENCY OF OCCURRENCE OF PRIMARY CARCINOMA OF THE APPENDIX.—This is difficult to ascertain statistically, because in most of the published reports of series of cases, in which the ap-

pendices were removed for some reason or another, there is not given the number of appendices which were examined systematically by the microscope; only such cases ought to be included in figures designed to show the relative frequency of primary cancers in removed appendices, because in a large number of cases in my series the tumors were not found except when sections had been examined under the microscope. Many of the appendices containing the cancers were considered at the time of the operations, when viewed macroscopically, to be tuberculous or to be merely the seat of simple cicatrices. The following are reported series of cases with the number of cancerous appendices in each; it is not mentioned in most of the reports just how many of the appendices were examined microscopically:

Baldauf.....	6 cancers in 735 appendices.
Neri.....	1 cancer in 82 "
Elting.....	2 cancers in 320 "
Jong.....	1 cancer in 255 "
Schrumpf.....	1 cancer in 150 "
Moschkowitz.....	6 cancers in 2000 cases.
Zaaijer.....	4 cancers in 463 "
Kelly (Deaver's cases).....	5 cancers in 2500 appendices.*
<hr/>	
Total.....	26 cancers in 6505 appendices or 0.4 per cent.

This frequency of cancer of the appendix differs from the conclusions of Baldauf and of Zaaijer, who maintain that such tumors occur in 1 per cent. of the cases of appendicitis. Their figures are based, however, on a much smaller number of cases than are mine. From my series above, this percentage of Baldauf is altogether too large. It is impossible to judge from the tabulated reports of the above-mentioned authors in what proportion of the cases microscopic examination of the appendices was made. Had such been made in all cases, it is not to be questioned that additional carcinomas would have been found. Until

* Personal communication from Dr. A. O. J. Kelly. Microscopic examinations were made of all these 2,500 appendices. Not included are two cases of endothelioma.

a large number of appendices are examined critically with the microscope, it will be impossible to ascertain correctly just what the true frequency of primary cancer of the appendix is. It is more than likely that many of the cases of cancer of the cecum are due to secondary extensions from a primary growth in the appendix. I have not included any such cases in my statistics.

AGE.—In 42 of my series of 48 cases, the ages are known, and are as follows:

					McWilliams.	Rolleston.	Total.	Per cent.
Between 1 and	10 years	2 cases		0	2	3	
" 10 "	20 "	9 "		7	16	20	
" 20 "	30 "	16 "		13	29	37	
" 30 "	40 "	11 "		7	18	22	
" 40 "	50 "	1 "		5	6	8	
" 50 "	60 "	1 "		2	3	4	
" 60 "	70 "	1 "		1	2	3	
" 70 "	80 "	1 "		0	1	1	
" 80 "	90 "			1	1	1	
—					—	—	—	—
Total.....					42 cases.	36	78	99
Average age 27.7 years.								

There were 2 patients aged eight years (Cases VI and X), 1 aged twelve (Case XXIV), 1 aged fifteen (Case XLIX). The oldest patient in my series was aged seventy-six years. It will thus be seen that 27 of the 42 cases, or 66 per cent., of primary cancer of the appendix in my series occurred before the age of thirty. The combined statistics of Rolleston and mine give 47 out of 78 cases, or 60 per cent., as occurring before thirty. The average age in the combined statistics is twenty-nine years.

This is in striking contrast to the age incidence in malignant tumors of the remainder of the intestinal canal. Thus, Rolleston gives, in 41 cases of primary cancers of the duodenum, the average age as fifty-two years; in 9 cases of primary carcinoma of the jejunum and ileum it was 47.2 years; in 30 cases of primary carcinoma of the cecum, 47.8 years; and in 100 cases of primary carcinoma of the remainder of the large intestine, 49.34 years. Thus, we find in 180 cases of cancer of the intestinal canal, exclusive of the

appendix, the average age is forty-nine years; while in 77 cases of primary cancers of the appendix the average age is twenty-nine years, which shows that the average age incidence in primary cancer of the appendix is twenty years less than in other parts of the intestine.

Mandlebaum reports that among 96 cases of primary cancer of the intestine occurring in the Mt. Sinai Hospital, New York, 5 were primary in the appendix, or 5.2 per cent. These cases constituted 0.75 per cent. of cancers from all sources. These are undoubtedly very high percentages of frequency, and cannot be accepted as generally typical.

From these statistics, it seems that the age incidence of primary cancer of the appendix corresponds somewhat closely to that of simple appendicitis. Thus, Deaver, in 3,000 cases of ordinary appendicitis, found the following to be the age percentages (I add the percentages in the cancer cases as contrast):

From			Simple appendicitis.		Cancer of appendix.
10 to 20 years		27.5	} or 69 p. c. before 30	23.0
" 21 to 30	"		41.5		37.1
" 31 to 40	"		20.1		21.8
" 41 to 50	"		7.0		7.6
" 51 to 60	"		2.8		3.8
" 61 to 70	"		0.6		2.5
" 70 to 80	"				1.2
" 80 to 90	"				1.2

SEX.—These were divided as follows:

	McWilliams.	Rolleston.	Total.	Per cent.
Females.....	24	20	44	57.1
Males.....	17	16	33	42.8

From these figures it appears that the disease occurs more frequently in women than in men, the difference in frequency being 15 per cent. in favor of the female sex. It has been suggested that this may be due to the more frequent performance of laparotomy in women than in men. In addition, the proximity of the appendix to the female generative organs, with the possi-

bility of extension to the appendix of irritation induced by inflammation of these organs, may have something to do with its greater frequency among women. Thus, in the 7 cases in my series in which cancerous appendices were removed in the course of other operations, 5 of these occurred in women, 4 of whom were operated upon for pelvic conditions. In Rolleston's 6 cases, operated upon for conditions other than appendicitis, 4 were for pelvic lesions. In a total, then, in Rolleston's and my own series of 13 operations, in course of which the appendices were removed, 8 were upon the female pelvic organs. This brings up the moot question, whether it would not be the part of wisdom in all cases to remove the appendix when one is operating in its vicinity.

Deaver found, in 3,000 cases of ordinary simple inflammations of the appendix, that 62 per cent. occurred in men and 38 per cent. in women. Many authorities maintain that ordinary inflammation in the appendix is the exciting cause of the development of primary cancers in them. If such ordinary inflammations occur in 62 per cent. of the cases in men and 38 per cent. in women, we should naturally expect that these primary cancers of the appendix would be more frequent in men; but the very reverse is the case, for 57 per cent. of primary cancers of the appendix occurred in women and 42 per cent. in men. What is the reason for this reversal of frequency in the two sexes in the two affections? At present there seems to be no explanation whatsoever that adequately answers this question; we must accept it as a fact, to be confirmed or rejected, as the case may be, later by a larger number of cases.

CONCRETIONS.—These were mentioned as being present in only 2 cases (X and XXXV). Rolleston found in his series of 42 cases that calculi were present in 3 cases. This makes a total of 5 cases out of 90, or 5.5 per cent. From this we may infer that concretions form a very small rôle, if any, in the etiology of cancer of the appendix, which is in striking contrast to the frequency with which calculi in the gall-bladder are found associated with primary cancer in that organ.

In only 1 recorded case of primary cancer of the appendix is there mention of a foreign body (other than coprolith) having been found. This is Case XXXV (Patel), in which a cancer and a small fish-bone were found in an appendix in an inguinal hernia.

The great rarity (5 per cent.) of fecal concretions in appendices containing primary cancers is in striking contrast to the frequency with which these bodies (not including other foreign bodies) are met with in operations for the removal of the appendix for ordinary inflammatory conditions. Thus, I have collected the following statistics with regard to the frequency of fecal concretions in ordinary appendicitis:

	Cases.	Fecal concretions.
Fitz.....	300	15
Ranvier.....	459	179
Murphy.....	141	43
Deaver.....	460	74
Schuylenburch.....	271	36
Hawkes.....	66	8
Hagen.....	184	21
Nordman (Korte).....	1522	608
Total.....	3403	984 (or 28.2 per cent.)

ENLARGED GLANDS.—These were mentioned as being present at the time of the operation in only 5 of the cases in my series, or 10 per cent., namely, Case I (Landau), VIII (Eccles), XXVIII (Barrow), XXVI (Wiener), XXVII (McCosh).

In Eccles' case, there were two small glands in the meso-appendix, which, unfortunately, were not examined microscopically. The later history of this patient is not given. In Barrow's case, the mesentery of the ileum, cecum, and part of the ascending colon contained ten or more, both palpably and visibly enlarged glands, one or two of them being as large as an adult thumb. They were deemed tuberculous at the time of the operation, being considered, erroneously, secondary to tuberculosis of the appendix. There was no microscopic examination of these glands. This patient is well at the present time, four years after the operation.

In Landau's case the meso-appendix contained one pea-sized gland, which, on microscopic examination, was found to be free from cancer. The later history of this patient is not given. In Wiener's case (XXVI), a large gland was removed from the mesentery near the ileocecal junction. Microscopic examination showed that it was free from cancer and was merely hyperplastic. This patient was well four years after the operation. In McCosh's case (XXVII), there were many large glands present, but the microscope proved these to be uninvolved by cancer. This patient was perfectly well nine years after the appendectomy.

In 2 cases in my series, Hartmann (XXXI), Baldauf (IV), there were small masses in the meso-appendix which at the time of the operations were considered to be enlarged glands, but which later, on microscopic examination, were found to be metastatic cancerous masses, secondary to the cancers in the appendices, and not cancerous glands.

In Rolleston's series of cases there were three patients in whom the abdominal lymphatic glands were enlarged (the cases of Fiske-Jones and Simmons, Beger, and A. O. J. Kelly). In the case of Fiske-Jones and Simmons, it was found by the microscope that the enlarged mesenteric glands were unaffected with cancer. The patient was well seven months after the operation. Beger's case did not survive the attempt to remove an iliac sinus, due to a cancerous appendix, which had existed for three and a half years. The fistula was found to lead directly into the appendix, which was infiltrated throughout by carcinoma, the growth projecting into the cavity of the cecum, but not actually involving its walls. On post-mortem examination, the retroperitoneal glands were found to have become implicated, but there was no suggestion that the growth in the appendix was other than primary. In the case of A. O. J. Kelly, the peritoneum was studded with very small grayish nodules which suggested miliary tubercles. The patient died on the sixth day as the result of an operation to replace protruding intestines. At the time of the primary operation

the retroperitoneal glands were found enlarged (apparently these were not examined microscopically).

Thus, out of 90 cases, only 8 had enlarged glands, or 9 per cent. Of these, in 4 cases the microscope showed that the enlarged glands were not implicated with cancer. In 3 cases the enlarged glands were not examined microscopically. In only one case (1 per cent.) was it positively demonstrated that the glands were cancerous. Hence we must infer that these cancers of the appendix are exceedingly slow in involving the lymphatics. As will be shown later, however, they do spread into the meso-appendix by direct continuity.

SITUATION OF THE TUMORS.—In 38 of the 48 cases in my series, this is found to be as follows (10 of the records are defective in this regard); Rolleston's series of 33 cases is also added:

	McWilliams.	Rolleston.	Total.	Per cent.
At or near the tip.....	26	16	42	59.15
In the middle.....	6	4	10	14.08
Near the base.....	2	8	10	14.08
At the middle and tip.....	1	1	2	2.81
Near the base and middle.....	1	0	1	1.40
Almost the whole appendix.....	2	4	6	8.44
Total.....	38	33	71	

From these figures we find that in over 59 per cent. of the cases the tumors were situated at or near the tip, and in 76 per cent. they were located at or distal to the middle. These are striking facts, since it indicates that primary cancers of the appendix develop in the regions where strictures, obliterations of the tip, and chronic inflammatory tissues occur most commonly. One can consequently scarcely refrain from arguing that there may be an etiological connection between these processes and the tumors. Such a relationship is further suggested by finding with the microscope that these cancers often develop directly in these pathological tissues, from which we may possibly infer that the cancer is a new implantation on a prepared ground. These regions, the seats

of predilection for cancers, are likewise most exposed to nutritional changes, due to malpositions and twistings, all of which conduce to decadence of tissues.

When all is said that can be said in favor of the view that the chronic inflammation is the precursor and cause of the development of the cancers, no one can deny that the reverse may be true, namely, that the cancer causes the chronic inflammatory changes. To this latter view, it may be objected that the chronic symptoms have, in many of the instances, existed for so long a period of time, years in some of the cases, as to make the existence of cancer for so long a period improbable. This objection, however, may be met by the statement that these primary cancers of the appendix are more than likely of very slow growth, particularly in the beginning. At present we are not in the position of being able to state positively which is primary, the cancer or the chronic changes in the appendix.

MACROSCOPIC APPEARANCE OF THE APPENDICES.—Information is afforded by a perusal of the records as to this point in 42 cases. The analysis shows some interesting results:

1. No tumor was present to the naked eye in 14 cases (33.3 per cent.) of the 42 cases. These were Cases 3, 4, 5, 6, 7, 9, 13, 15, 18, 19, 33, 37, 42, 43.

2. A cyst was present in 3 cases (0.7 per cent.); size (a) small, No. 20; (b) bean, No. 1; (c) large, No. 29 (4 inches long by 2½ wide, with a twisted pedicle).

3. One or more solid tumors were present in 23 cases (55 per cent.). (a) Single tumor, 19 cases: size (1) small, 4 cases, Nos. 24, 25, 36, 39; (2) pea, 13 cases, Nos. 2, 10, 12, 14, 16, 21, 23, 26, 30, 31, 44, 49; (3) bean, 2 cases, Nos. 17, 45. (b) Two tumors, 3 cases, Nos. 8, 28, 32. (c) Numerous tumors, 1 case, No. 35.

4. Clubbed tip only, 2 cases, Nos. 11 and 34.

5. In 9 cases there were found obliterated areas ("cicatrices") which later under the microscope were discovered to be cancerous cicatrices. These were Cases 3, 5, 7, 14, 21, 25, 33, 36, 37.

6. In 2 cases ulcers were present, Nos. 4 and 6. In both of these cases cancers were found in the ulcers themselves.

7. Perforations were present in 2 cases, Nos. 10 and 22, and concretions were found in 2 cases, Nos. 10 and 35.

8. Four of the cases, all of which had visible small tumors, were thought at the time of the operation to have tuberculous appendices. These were Cases 8, 10, 28, 31. The microscope alone revealed their true nature.

This analysis is interesting to the operating surgeon, for in only 55 per cent. of the cases were visible tumors present. Many of these tumors, however, could not be seen from the outside, as the growths often projected into the lumen without any external prominences, as was instanced in my own case (XXII). In 14, or 33 per cent., no tumors were visible to the naked eye, even after the appendices had been opened throughout. Three of the appendices before they were cut open were erroneously thought to have diverticula as the cause of the prominences at the time of the operations.

From these statistics, then, it is easily seen how fallacious it is to argue that because there is no visible tumor there can be no cancer present; only by careful microscopic examination can possibility of cancer be excluded. Hence the inaccuracy of any statistics based solely on the macroscopic appearances alone of the appendices.

PATHOLOGICAL CLASSIFICATION OF THE TUMORS.—This is a somewhat difficult task, by reason of the different aspects in which this part of the theme has been considered, and on account of the use of a widely varying nomenclature by the authors. I have been assisted in this division by Dr. F. C. Wood, of the Pathological Department of Columbia University, New York, to whom my thanks are due for the assistance, as well as for the photomicrographs which accompany this article.

The following divisions of the neoplasms have been made, based on the microscopic examinations. There are 71 cases in which such examinations are reported:

1. *Columnar-cell Tumors*.—Among these I have also included those which in the records are called adenocancers, cylindrical-cell cancers, and alveolar cancers. There were 14 of this type, or 33 per cent. of the 42 cases in which the variety of cancer was stated in my series of 48 cases. These were Cases 2, 3, 12, 21, 26, 29, 30, 31, 32, 37, 43, 46, 47, 48. The age and sex are stated in 11 cases:

6 females, average age, 39.5 years. 1 was 76 and another 63.

5 males, " " 30.5 years. 2 were 35.

11 average age, 35 years.

2. *Spheroidal-cell Cancers*.—Among these are included scirrhus cancers, solid globo-cellular cancers, basal-cell cancers, cancer simplex, polyhedral-cell cancers, carcinoma solidum diffusum, polymorphous-cell, and round-cell cancers. Of these there were 22 cases, or 52.4 per cent. of the 42 cases in my series, in which the variety of neoplasm is stated.

15 females, average age, 23.6 years.

7 males, " " 23.4 "

22 average age, 23 years.

These cases were Nos. 1, 4, 5, 6, 7, 8, 10, 13, 15, 18, 19, 20, 22, 24, 25, 27, 33, 34, 36, 44, 45, 49.

3. *Mixed Types*.—Four cases, 1 male, 3 females; average age 29.7 years. (a) Scirrhus cancer with intimation of adenocancer, No. 11, male, aged thirty-five years. (b) Cancer solidum alveolare partim solidum diffusum, No. 14, female, aged thirty-five years. (c) Partly adenocancer, partly cylindrocellulare solidum, partly carcinoma solidum diffusum, No. 16, female, aged twenty-six years. (d) Partly adenomatous, chiefly solid and diffuse, No. 23, female, aged twenty-three years.

4. *Columnar-cell cancer*, undergoing spheroidal-cell transformation, 1 case, No. 9, age and sex not given.

5. *Colloid Cancer*.—Case No. 17, male, aged twenty-five years.

6. *Endothelioma*.—None in my series.

7. "*Cancer*" the only designation. Cases 28, 35, 39, 40, 41, 42. Total, 6 cases. In only 3 of these 6 cases are the ages and sex given. There were 2 males with an average age of thirty-eight years and 1 female of seventeen years.

COMBINED STATISTICS,

	McWilliams.	Rolleston.	Totals.	Per cent.	Average age.
Columnar-cell cancers.....	11	5	16	22.5	43.5
Spheroidal-cell cancers.....	22	16	38	53.5	23.5
Transitional cancers.....	1	6	7	9.8	32.7
Mixed cancers.....	4	0	4	5.6	29.7
Colloid cancers.....	1	2	3	4.2	
Endotheliomas.....	0	3	3	4.2	
Total.....	39	32	71		32.3

From these statistics we see that the spheroidal-cell cancers are 30 per cent. more frequent than the columnar-cell types. There is also a difference of twenty years in the average age incidence in the two varieties of cancer, the average age in the spheroidal-cell cancers being twenty-three years and in the columnar-cell type forty-three years.

If we compare the frequency of these various types of cancer in the remaining portions of the alimentary canal, we find the following to be the case in this regard:

Peterson and Colmers:

Large intestine:

	Per cent.
Adenocancer.....	86.5
Spheroidal cell.....	13.5

Kappers and Van Rooyen:

Stomach and intestines:

	Per cent.
Adenocancer.....	56.6
Mixed forms.....	13.2
Spheroidal cell.....	20.7
Colloid.....	9.5

Intestines alone:

Adenocancer.....	72.7
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If we compare these figures with those showing the frequency of the different types in appendical cancers, we have a striking contrast.

	Stomach with intestine. Per cent.	Large intestines. Per cent.	Intestines alone. Per cent.	Appendical cancers. Per cent.
Adenocancers.....	56.6	86.5	72.7	22.5
Spheroidal-cell cancers.....	20.7	13.5		53.5
Colloid cancers.....	9.5			4.2
Mixed cancers.....	13.2			5.6

Hence we see that in the appendical cancers, the columnar-cell, or adenomatous cancers, occur in about one-quarter of the cases only, while in the direct intestinal tract this type of cancer is the rule, occurring in almost three-quarters of the patients. In the stomach and intestines, taken together, the spheroidal-cell cancer is found in only one-fifth of the cases, while in the appendix this type of cancer is found in over one-half of the cases. Colloid cancers of the appendix seem to be rarer than in the other portions of the intestinal tract.

What the significance of these observations is I do not pretend to be able to state or even to speculate about.

A rather striking similarity between the frequency of the occurrence of the various forms of the stomach and appendical cancers is shown when we compare the statistics on this point of 115 cases of stomach cancer reported by Fenwick and the 71 cases of appendical cancers in my series:

	Stomach cancer. Per cent.	Appendical cancer. Per cent.
Columnar-cell.....	28.6	22.5
Spheroidal-cell.....	63.3	53.5
Colloid cancer.....	7.8	4.2

MICROSCOPIC EXTENT OF THE GROWTHS.—Of the 48 cases in my series, there are records regarding this point in 31 cases, as follows: The neoplasm extended through the mucosa and submucosa alone in 4 cases, or 12.7 per cent., Cases 6, 12, 30, 37. Through the mucosa, submucosa, and muscularis only in 8 cases, or 25.8 per cent., Cases 10, 14, 15, 18, 22, 24, 29, 32. Through

the mucosa, submucosa, muscularis, and subserosa in 4 cases, or 12.7 per cent., Cases 5, 11, 17, 33. Through all coats without involvement of the meso-appendix in 8 cases, or 25.8 per cent., Cases 1, 7, 19, 20, 21, 25, 27, 34. Through all the coats with involvement of the meso-appendix in 7 cases, or 22.5 per cent., Cases 3, 4, 13, 16, 23, 28, 31.

From these statistics, then, we find that these appendical neoplasms, when viewed histologically, have a malignant character, showing a tendency to infiltrate progressively contiguous structures (15 cases out of 31, or 48.4 per cent., involving all the coats of the appendices), but without, however, evincing evidences of producing distant metastases or of affecting neighboring lymphatic glands. This invading characteristic is evidently of slow progress, fortunately for the patients. This slow growth is further evidenced by the scarcity of mitotic figures in the sections. In no case are they mentioned as being abundant, the usual designation being "very few."

The malignancy of any tumor is to be judged rather from a clinical than a histological standpoint. Thus we find that rodent ulcer when viewed from a microscopic aspect is a typical carcinoma, and that epulis is a typical sarcoma, yet each clinically has repeatedly been proved to be a fairly benign tumor. The question, then, which particularly interests the operating surgeon is what is the ultimate fate of the patients from whom primary cancers of the appendix have been removed?

DURATION OF REPORTED CURES.—The after-histories of a number of the patients have been recorded, and the durations of the cures in the following instances are given:

Well after 9	years,	2 cases,	Jalaguier, McCosh.
" "	5½	" 1 case,	Driessen.
" "	5	" 3 cases,	Rolleston, H. Kelly (2 cases).
" "	4	" 3 "	Wiener, Lecene, Fauldner.
" "	3	" 4 "	Wier, Warthin, Cullingworth and Corner, Zaaier.
" "	2	" 8 "	Moschkowitz, Eccles, Hurdon, Zaaier, Mandlebaum, Greig, Jong, Thorndike.

Well after 1½ years, 4 cases, Moschkowitz, Zaaier (2 cases), McBurney.

" " 1 year, 2 " Battle, Burnham.

" " 7 months, 2 " Zaaier, Jones and Simmons.

" " 6 " 1 case, Zaaier.

30 cases.

Of the 90 cases in the two series, there were 79 cases operated upon. Of these, 13 were well three years or more after the operations, or 16 per cent., and 21 were well two years or more after the operations, or 26 per cent. Of course, many of the operations were of recent date, and the permanency of the cures is still sub judice.

PROGNOSIS.—It is a remarkable fact that primary cancer of the appendix, which microscopically appears to be a malignant growth, is a relatively benign tumor when viewed clinically, since it does not tend to involve the lymphatics nor to form metastases. Recurrences after operation are almost unknown. This apparent benignity seems to be an exception to the rule that the younger the patient with a malignant growth, the more malignant is that growth. This must simply be accepted as a fact without adequate explanation. Cullingworth and Corner, and also Battle, suggest that perhaps the accompanying inflammation destroys the growth by the sloughing of the offending organ, or the patient dies from peritonitis, or the growth is removed because of the coincident inflammation before dissemination occurs. It must further be remembered that when these growths have become extended, as undoubtedly occurs, they lose all their characteristics as appendical neoplasms, and they are then recognized as cecal cancers only.

In the 79 patients making up the series of Rolleston and my own, who were operated upon, there was only 1 (1.2 per cent.) in which the growth is definitely known to have recurred. This is the case of Lejars. A secondary operation, four months after the first one, showed a cancer of the cecum. The patient succumbed shortly afterward.

An interesting case is related by Lanz¹ of a probable recurrence after operation of a primary cancer of the appendix. It is not included in my series, because there was no microscopic examination of the appendix at the time of the operation. A man, aged forty years, suffered from symptoms of chronic appendicitis. At the operation, the appendix was found adherent and its tip was swollen like a "drumstick." A section of the appendix showed at this latter point a hard tissue mass, which was considered to be a "scar." A recurrence took place, and it was by this only that the true carcinomatous nature of the "scar" was recognized. A similar case is described by De Ruyter², in which at autopsy a carcinoma was found to have developed in the stump of an appendix which had been removed six years previously. This case, for a like reason, is not included in my series.

Secondary growths, including cancerous lymphatics, were recognized as occurring in very few cases. In my own series of 48 cases there were only 2 in which mention is made of any such. These were patients of Hartmann (XXXI) and Baldauf (IV), in each of which there was a small metastatic cancerous mass in the meso-appendix. In Rolleston's series of 42 cases there were 4 such cases, namely, Beger's patient, in whom the retroperitoneal glands were implicated, the 2 patients of A. O. J. Kelly and of Elting, in both of whom there were multiple growths on the peritoneum, and Whipham's patient (autopsy), in which there were growths in the liver and right ovary. Thus, we find that in only 6 cases out of 90 in the combined statistics of Rolleston and myself, or 6 per cent., were there secondary growths. From the analysis of the cases in a preceding paragraph, in which there were enlarged glands at the time of the operations, it is seen that because glands are found enlarged, this is no reason for making a bad prognosis, since the microscope showed that only 1 case had cancerous lymphatics, the remainder being merely affected secondarily by simple inflammation from the appendices. Perhaps we may conclude, from the fact that fewer secondary growths were found in my series

of cases than in Rolleston's, that appendices are removed more frequently now than formerly was the case for chronic symptoms, and at an earlier date and for slighter symptoms. By so doing, we undoubtedly will in future save a number of patients from developing cecal cancers, secondary to a primary growth in the appendix.

From the facts thus far deduced, it seems as though we should have to place these primary neoplasms of the appendix in a distinct class by themselves, so far as their malignancy is concerned, allying them somewhat in this regard with rodent ulcer and epulis, and in contradistinction to neoplasms of the alimentary tract generally.

MORTALITY OF THE OPERATIONS.—All the patients in my series recovered after being operated upon, indicating that the presence of primary appendical cancer does not prejudice the operative prognosis *per se*.

SURGICAL SIGNIFICANCE OF APPENDICAL CANCERS.—These small neoplasms are not *per se* to be diagnosticated before operation. The symptoms are those of a simple appendicitis, usually of the chronic, recurrent type. Its age incidence corresponds to that of simple appendicitis. It probably occurs in about 0.4 per cent. of all cases of appendicitis, or 1 in 250, and this fact, if further confirmed in the future, will more surely cause us to advise appendectomy. The seemingly good prognosis of appendical cancers is more apparent than real, for histologically it has a malignant character with a tendency to involve progressively, though probably slowly, the meso-appendix and the cecum. Whether the cancer is the primary lesion and the appendicitis the secondary, or vice versa, makes absolutely no difference from the patient's standpoint. The main thing for him is to be rid of his cancerous appendix at the earliest possible moment.

Such an appendical cancer will almost always first be discovered by an operation. Benign tumors of the appendix are very rare, hence any circumscribed appendical tumor, found at opera-

tion, should always make one suspicious of cancer. In doubtful cases, a frozen section, made during the operation, would be of very great advantage, if possible to obtain; and in case of positive findings, a wide excision of the meso-appendix and removal of the lymphatic glands should be practised. If the tumor be situated in the base of the appendix, it would be best to excise part of the cecum, otherwise this would not seem ordinarily to be a necessary procedure. As a frozen section at the time of the operation will rarely be available, it would be the part of wisdom to make a practice of removing habitually the entire meso-appendix in every operation for appendicitis, as this would not increase materially the risk to the patient under ordinary conditions. This practice is rendered advisable, first, because these tumors, even when very small, have a pronounced tendency to invade the meso-appendix; and second, because they frequently are invisible to the naked eye. Every removed appendix should be subjected to a careful microscopic examination.

When operating in the neighborhood of the appendix for reasons other than appendicitis, the appendix should be inspected carefully. If it has an irregular outline, or is clubbed at its extremity, or constricted, or presents a prominence on its surface, it should unhesitatingly be removed. I shall not go into the more debatable question of whether, in operations generally, the appendices should be routinely amputated in the absence of any visible abnormality. It seems, however, advisable to do so provided no extra risk would be incurred, since the appendix is such a potential factor for future harm for the patient in many directions. The practice of removing the appendix close to its junction with the meso-appendix should be deprecated.

RÉSUMÉ.—1. Of the 76 patients operated upon for known reasons, 63 (83 per cent.) suffered from some variety of appendicitis. Of these, 23 (36 per cent.) were operated upon during or immediately after the first acute attack, while 40 patients (63 per cent.) had had symptoms of chronic appendicitis for varying

periods of time. Of the entire 79 operated patients, 28 per cent. had had such chronic symptoms for a year or more. Eleven primary cancers of the appendix were found in appendices removed in the course of operations for other purposes, and were chance findings. In 2 other cases, the operations were undertaken for the cure of iliac fistulæ. Ten primary cancers of the appendix were found in the course of autopsies.

2. In 78 cases in which the ages are recorded, it is found that there are 47 patients (60 per cent.) whose age was under thirty years. This age incidence corresponds very closely to that of ordinary inflammatory appendicitis, in which, in 3,000 cases, 69 per cent. occurred before thirty years.

3. In 77 cases of primary cancer of the appendix in which the sex is recorded, we find that there were 44 females (57 per cent.) and 33 males (42 per cent.). In 3,000 cases of simple, inflammatory appendicitis, 62 per cent. occurred in men and 38 per cent. in women. The reason for this almost complete reversal of frequency in the two sexes in the two affections remains as yet entirely unexplainable.

4. Concretions apparently form no rôle in the etiology of primary cancers of the appendix, since in 90 cases they were found only 5 times (5.5 per cent.). This is in sharp contrast to the 984 times fecal concretions were recorded as occurring in 3,403 operations for simple inflammatory appendicitis, or 28 per cent.

5. In 71 cases in which the situation of the tumors was recorded, it is found that in 59 per cent. the neoplasms were located at or near the tip, and in 76 per cent. they were situated at or distal to the middle. This indicates that primary cancers of the appendix develop in the regions where strictures, obliterations of the tip, and chronic inflammatory lesions most commonly occur.

6. Enlarged lymphatic glands were recorded as being present in 8 cases, or 9 per cent. In 4 of these cases, microscopic examinations showed that there was no cancer in them, and in 1 case such

secondary cancerous involvement was found. Hence we must infer that these primary cancers of the appendix are exceedingly slow in involving the lymphatics. Three cases are not recorded as having had the enlarged glands examined microscopically.

7. In 42 cases out of my 48 in which it is recorded, no tumors were visible to the naked eye in 14 cases, or 33 per cent. In 23 cases, or 55 per cent., one or more solid tumors were visible. Cysts were present in 3 cases, or 0.7 per cent. Perforations were present in 2 cases. Ulcerations were found in 2 cases. From these statistics it is evident how fallacious it is to argue that because there is no visible tumor, consequently there is no cancer present. Hence the inaccuracy of any statistics based solely on the macroscopic appearances of the appendices.

8. The frequency of occurrence of primary cancer of the appendix is approximately shown in the fact that 26 such cancers were found in 6,505 appendices, or 0.4 per cent. This percentage is not absolute, because it is not stated in just what proportion of these cases microscopic examination of the appendices was made; presumably such examinations were made in but a small proportion. In addition, cecal cancers undoubtedly develop from primary appendical cancers, in which case the latter lose all their characteristics as the primary lesion, and are overlooked as such. From all of which we may conclude that a conservative estimate would place the occurrence of primary cancer of the appendix as not lower than 0.4 per cent. of all the appendices removed, or 1 in every 258 appendices examined. Positive proof of this estimate can only be established when a large series of microscopically examined appendices is brought forward.

9. In 71 cases it was possible to make a pathological classification of the neoplasms. Twenty-two per cent. were columnar cell cancers, 53 per cent. were spheroidal-cell, 9 per cent. were of the transitional type, and 4 per cent. were colloid cancers. The average age in the spheroidal-cell tumors was twenty-three years

and in the columnar-cell type it was forty-three years, a difference in the age incidence in the two varieties of twenty years. Thus, we see that the spheroidal-cell cancers, primary in the appendix, are 30 per cent. more frequent than the columnar-cell variety. The frequency of occurrence of the two varieties in the appendix is very similar to that in neoplasms of the stomach, while in the intestines alone the columnar-cell type occurs in about 72 per cent. of the cases.

10. Of the 48 cases in my series, there are records regarding the microscopic extent of the growths in the appendices in 31 cases. In 15 cases, or 48 per cent., all the coats of the appendix were invaded, while in 7 cases, or 22 per cent., the meso-appendix in addition was involved in the growth. Thus these neoplasms show a tendency progressively to infiltrate contiguous structures, but without evincing evidences of producing distant metastases. This invading characteristic is probably of slow growth, as is further evidenced by the fact that in all the cases mitotic figures are designated as being very few.

11. Out of 90 patients with primary cancer of the appendix, there were secondary growths present in 6 (6.6 per cent.).

12. In 79 of the patients who were operated upon, the duration of the reported cures is given in 30 instances: 7 patients were well five years or more after the original operations, 13 were in good health three years or more afterward, while 21 showed no signs of any recurrence two years or more after the operations. In only 1 instance out of the 79, or 1.2 per cent., is it definitely stated that the growth recurred. From the facts deduced in this article, it would seem as though these primary tumors of the appendix should be placed in a distinct class by themselves, so far as their malignancy is concerned, allying them somewhat in this regard with rodent ulcer and epulis, and in contradistinction to malignant neoplasms of the alimentary tract generally.

13. The mortality in my series of 46 operations was nil, which indicates that the presence of a primary appendical cancer does not prejudice the operative prognosis per se.

14. The symptoms of these appendical cancers are not sufficiently characteristic to make a diagnosis per se possible without operation.

15. Any circumscribed tumor in an appendix should always arouse suspicions of cancer, following which the meso-appendix should be widely excised and enlarged glands removed. It will be necessary to excise part of the cecum only when the tumor is situated in the base of the appendix.

16. In every appendectomy the entire meso-appendix should be removed if possible.

17. Every removed appendix should be examined microscopically.

18. When operating in the neighborhood of the appendix for reasons other than appendicitis, the appendix should be amputated in case it presents any abnormality, particularly when its tip is clubbed.

19. In addition to the cancers themselves present in the appendices, in 30 cases out of 48 in my series, or 62 per cent., it is found that chronic inflammatory lesions were discovered by the microscope. Whether the chronic changes are primary and the cancers secondary to these, or vice versa, it seems impossible to decide in the present state of our knowledge of the subject.

ADDENDUM.

Since the above article was written, I have found the following additional 33 cases.

Letulle³ has written a very beautifully illustrated article describing 11 cases which he personally has seen. Two of these are reported in the above article, namely, those of Jalaguier and Nelaton, while the remaining 9 are not so included. Of these 11 cases, only four cancerous appendices were removed at operation, while seven were discovered at autopsy. It is a noteworthy ob-

servation that 4 of these latter cases were found in tuberculous patients⁴. Some of these cases illustrate unusual conditions.

Gayet⁵ reports a case in which a cancerous appendix was found in a hernial sac, exactly similar to the condition narrated in Patel's case in the above article.

Vassmer⁶ relates a case of primary cancer in a gangrenous appendix with peritonitis. The patient died after a secondary enterostomy.

Lubarsch⁷ reports the case of a seventeen-year-old boy in the tip of whose appendix, at autopsy, a pea-sized cancer was found.

Weber⁸ reports the case of a man, aged forty-three years, who was operated upon for the removal of a ventral hernia, following an operation three years previously for a large appendical abscess. A fist-sized tumor was found in the cecal region which proved to be an adenocancer of the appendix. Recovery.

Lothrop⁹ reports operating upon a girl, aged nine years, for an acute gangrenous, perforative appendicitis, with abscess formation. On gross examination, nothing unusual was noticed in the appendix, but later microscopic examination revealed in its centre a primary cancer. The patient recovered. Her youth is noteworthy.

White¹⁰ reports a case of colloid carcinoma of the appendix.

LeConte¹¹ reports a case in which the entire appendix was invaded by the cancer with involvement of the ileocæcal glands.

Coons¹² found a spheroidal-celled carcinoma of the appendix in a woman of twenty-one years of age. The appendix was removed in the course of an operation for pyosalpinx and ovarian abscess, because it seemed to contain a concretion which could not be dislodged. At the distal end there was found a pea-sized, nodular mass, which was firmly imbedded in the wall of the appendix.

Hammond¹³ reports an infiltration carcinoma in the appendix of a man, thirty-five years of age, who was in his eighth attack of appendicitis, the first of which dated back thirteen months.

Garrow and Keenan¹⁴ report two cases, one of which would

not have been discovered but for routine examination. One was found in a perforated, gangrenous appendix with abscess.

Monk¹⁵ removed an appendix because of appendicitis, there being no suspicion as to malignant disease until the report of carcinoma of the appendix was returned by the pathologist. There has been no recurrence five and one-half years after the operation.

Harte¹⁶ reports eight cases not given above. In addition he gives résumés of six cases of sarcoma of the appendix.

Day and Rhea¹⁷ publish a case of primary cancer of the appendix in a child, nine years of age.

Elwell¹⁸ describes a case of primary cancer of the appendix, likewise Kepler¹⁹ who gives the literature.

The following unpublished case is kindly given to me by Dr. J. A. Hartwell. He operated upon a woman of thirty-three years of age at the end of her second attack of appendicitis. The appendix was clubbed and inflamed and adherent at the tip. There was no suspicion awakened at the time of the operation of malignancy. There were no enlarged glands. Pathological report: The appendix measured 9 by 1 cm. Serous coat injected. On section canal free, but walls thickened. At tip is a small yellowish growth, occupying the lumen, $\frac{1}{2}$ cm. in diameter. Microscopical examination. There is a growth of fat and connective tissue in submucosa. The mucosa and submucosa of sections from the tip are infiltrated with large, round and oval cells in nests and strands. Diagnosis is carcinoma of appendix.

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VIII.

A CONTRIBUTION TO OUR KNOWLEDGE OF THE ACETONE BODIES, WITH A CLINICAL METHOD FOR THE QUANTITATIVE ESTIMATION OF DIACETIC ACID AND ACETONE.*

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(To this Essay was awarded the Briddon Prize Medal for 1907.)

The scientific and clinical importance of the acetone bodies, viz.: acetone, diacetic and oxybutyric acids, is demonstrated by the many investigations which have been lavished upon them in the last decade. As evidences of disordered metabolism they are of significant value.

The Germans have been the leaders in this promising field of research, but many valuable studies have come from our own countrymen, among which may be recalled the work of Herter, Joslin, Brewer, Baldwin, Hubbard, Brackett, Stone, Low and others.

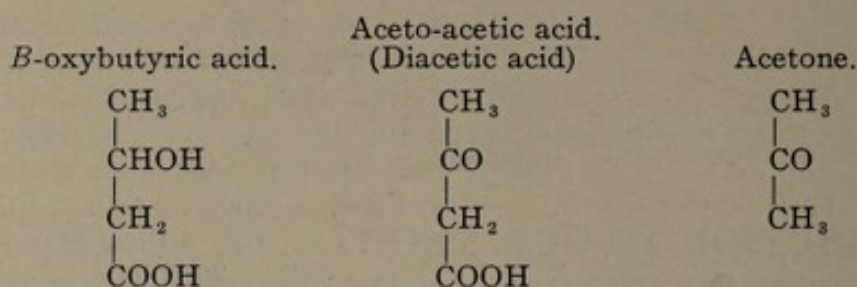
While much of the earlier work led to conclusions more or less contradictory, the more recent observations permit us to co-ordinate our knowledge and are full of promise for a rational system of prophylaxis and therapy.

It seems worth while, therefore, to review some of the facts as we know them to-day.

THE RELATION OF THE ACETONE BODIES TO ONE ANOTHER.

The relationship of the acetone bodies is a result of their chemical constitution and is made evident by examining their graphic formulæ.

* Reprinted from the Archives of Internal Medicine, February 15, 1908.



By oxidizing oxybutyric acid we obtain diacetic acid, and when diacetic acid is heated to 100° C. it is readily decomposed into acetone and carbonic acid. The latter reaction occurs so readily that hitherto no satisfactory method has been devised of separating the acetone and diacetic acid of the urine, and therefore all quantitative estimations of acetone represent the combined output of diacetic acid and acetone.* By a laborious process we are able, however, to estimate separately the amount of oxybutyric acid.

It seems to be established that oxybutyric acid is the antecedent body from which diacetic acid and acetone are formed. Schwartz¹ has given diacetic acid by mouth to diabetic animals and has seen a partial conversion into acetone in the urine. Geelmuyden² gave sodium salts of diacetic acid to normal men, who were on a mixed diet, and a diet without carbohydrates, and found an increase in the acetone output in each instance. Minkowski³ gave a dog with pancreatic diabetes ten grams of sodium oxybutyric acid, obtaining as a result a large amount of diacetic acid and acetone in the urine.

The relationship of the acetone bodies is also evident, when we consider the order in which they make their appearance in the urine. For example, in a progressive case of diabetes mellitus the first of these bodies which we find is acetone, as the process advances we next detect diacetic acid, and when diacetic acid has increased to a considerable amount oxybutyric acid appears. When a bad case of diabetes begins to improve the acetone bodies

* Recently Follin has proposed a new method for the separation of acetone and diacetic acid (Jour. of Biol. Chem., May, 1907). From a somewhat limited experience with this method, I am inclined to the conclusion that it determines approximately the actual quantitative relationship of these bodies.

disappear in the inverse order in which they occurred; oxybutyric acid is the first to go, followed by diacetic acid and finally by acetone. These sequences, ascending and descending, indicate, respectively, the progressive failure and improvement of oxidation.

Arnold⁴ thinks that all the acetone of the urine is excreted as diacetic acid, which is converted into acetone in the urine. He reached this conclusion because, whenever he found acetone in the urine, he also found diacetic acid by means of the test which bears his name. I think his conclusion is incorrect, and that he was led into this error by making use of the comparatively indelicate test of Legal in determining the presence of an acetonuria. As the following table will demonstrate, in a number of my cases I have been able to detect and estimate the quantity of acetone in the urine, without being able to detect diacetic acid either by Gerhardt's or Arnold's reaction, the latter being the most delicate test for diacetic acid which we possess.

CASES SHOWING PRESENCE OF ACETONE WITHOUT DIACETIC ACID.

Case	Date of Examination	Diagnosis	Acetone		Diacetic Acid			
			Lieber's Test	Quantity in Grams	Arnold's	Gerhardt's	Diazo	Riegler's
E. W.	14-IV-'05	Cyclic vomiting	+	0	0	0	0
L. B.	16-V-'05	Diabetes	+	0	0	0	0
A. C.	12-IV-'05	Diabetes	+	0	0	0	..
B. B.	13-IV-'05	Diabetes	+	0	0	0	..
E. A. S.	15-IV-'05	Diabetes	+	0	0	0	..
C. C. K.	15-IV-'05	Diabetes	+	0	0	0	0
	25-V-'05	Diabetes	+	0.018	0	0	0	..
L. H.	7-VI-'05	Diabetes	+	0.021	0	0
M. E. M.	9-V-'05	Diabetes	+	0.017	0	0	0	0

Further, as regards Arnold's contention, it may be said that in diabetes and other conditions a large amount of acetone is found in the breath and diacetic acid is not found in the expired air; therefore it would seem probable that acetone is present as

such in the circulating blood and hence would be excreted as such by the kidneys.

When, however, acetone appears in any considerable amount in the urine, diacetic acid can always be detected, and when in turn diacetic acid is evident in large quantities, as for example when we have an exceedingly strong Gerhardt's reaction, oxybutyric acid is always found.

TABLE SHOWING APPEARANCE OF DIACETIC ACID WHEN ACETONE IS EXCRETED IN CONSIDERABLE QUANTITIES.

Case	Date of Examination	Diagnosis	Acetone Tests		Diacetic Acid Tests				Amount of Acetone in 24 hours in grams	Rotation	
			Lieber's	Legal's	Arnold's	Gerhardt's	Diazo	Riegler's		Before fermentation	After fermentation. Indicating presence of Oxybutyric acid
C. C. K.	25-V-'05	Diabetes	+	0	0	0	0.018
M. E. M.	9-V-'05	Diabetes	+	0	0	0	..	0	0.017
L. H.	7-VI-'05	Diabetes	+	?	0	0	0.021x
B. B.	25-IV-'05	Diabetes	+	+	0	0	0.037x
C. C. K.	27-IV-'05	Diabetes	+	+	0	0.060
L. B.	10-V-'05	Diabetes	+	+	+	0	0	0	0.068
C. C. K.	13-VI-'05	Diabetes	+	+	+	0	0	0	0.399
F. J. M.	8-VI-'05	Diabetes	+	+	+	0	0	..	0.160x
G. L.	1-V-'05	Diabetes	+	+	+	+	+	..	0.800
S. C.	5-V-'05	Diabetes	+	+	+	+	+	..	0.616
G. L.	15-V-'05	Diabetes	+	+	+	+	+	?	0.657
G. L.	5-VI-'05	Diabetes	+	+	+	+	+	?	1.113
S. B. C.	3-V-'05	Diabetes	+	+	+	+	+	..	1.111x
G. L.	8-V-'05	Diabetes	+	+	+	+	+	+	1.333x	+0.5	-1.2
J. F.	12-II-'04	Diabetes	+	+	+	+	+	..	0.292	+6.0	-1.0
J. F.	22-II-'04	Diabetes	+	+	+	+	0.962	+6.8	-0.4

+ positive reaction, ? doubtful reaction, 0 negative reaction, x amount in one liter.

I think we may look upon the excretion of oxybutyric acid and diacetic acid as invariably due to pathological conditions, and the appearance of any considerable amount of acetone must be regarded in the same light.

CONDITIONS IN WHICH ACETONE BODIES OCCUR.

Recent observation has demonstrated that the excretion of the acetone bodies occurs in a wide number of diseases and under many conditions. In very small amounts acetone may be excreted in the urine in health under normal conditions. v. Engel⁵ puts the normal limits at from 0.006 to 0.018 gram of acetone in twenty-four hours. In pathological conditions acetone is thrown off in the expired air as well as in the urine, but diacetic and oxybutyric acids cannot escape by way of the lungs and are excreted by the kidneys alone. There seems to be no constant ratio between the amount of acetone excreted by the kidneys and by the lungs. Schwartz,⁶ in some of his determinations, found 70 per cent. of the acetone in the expired breath. The acetone bodies are excreted in considerable quantity in starvation; in certain digestive disturbances; in many febrile diseases such as exanthemata, pneumonia and typhoid fever; after surgical operations; during pregnancy and labor; after the administration of certain drugs, among which are benzol, antipyrin and morphine; following poisoning with phosphorus, phloridzin, atropine, coal gas, curare and lead; in diabetes their amount may be very large. Naunyn⁷ reports a case in which there was an output of 188 grams of sodium oxybutyric acid in a single day.

The following table will indicate the various conditions under which acetone bodies are excreted, with the maximum amounts, as noted by numerous observers:

CONDITIONS UNDER WHICH THE ACETONE BODIES ARE EXCRETED.

Condition or Disease	Acetone	Diacetic Acid	Maximum amount of Acetone in twenty-four hours. Estimations include Diacetic acid		Oxybutyric acid	Amount of Oxybutyric acid in twenty-four hours	Observer
			Urine	Breath			
Normal	+	0.010	v. Jasch.
Normal	+	0.015	Boeri.
Normal	+	0.018	v. Engel.
Normal	+	0.023	Müller.
Starvation	+	0.703	Hirschfield.
Starvation	+	0.784	Müller.
Starvation	+	+	+	2.98	Waldvogel.
Starvation	+	+	0.699	+	1.60	Waldvogel.
Starvation	+	0.431	0.469	Joslin.
Starvation and oleic acid	+	0.926	0.847	Joslin.
Digestive disturbances	+	+	+	Lorenz.
Diarrhoea	+	+	+	Magnus-Levy.
Auto-intoxication	+	+	4.000	Beauvy.
Appendicitis	+	+	0.500	Beauvy.
Typhoid	+	+	0.400	Beauvy.
Typhoid	1.000	Beauvy.
Erysipelas	+	+	+	v. Noorden.
Variola	+	+	0.800	Beauvy.
Varicella	+	+	0.500	Beauvy.
Measles	+	+	0.600	Beauvy.
Measles	0.800	Beauvy.
Scarlatina	+	+	+	Külz.
Otitis	+	+	0.700	Beauvy.
Diphtheria	+	+	0.500	+	Beauvy.
Pneumonia	+	+	0.700	Beauvy.
Tubercular meningitis	+	+	1.000	Beauvy.
Anæsthesia	+	+	0.600	Beauvy.
Diabetes mellitus	+	+	0.600	+	Waldvogel.
Diabetes mellitus	+	+	10. +	Naunyn.
Diabetes mellitus	+	+	19.000	Magnus-Levy.
Diabetes mellitus	+	+	4.200	3.600	Schwartz.
Diabetes and mixed diet	+	+	+	12.1	Wolpe.
Diabetic coma	+	+	+	22.8	Wolpe.
Diabetic coma	+	+	+	16.0	Minkowski.
Diabetic coma	+	+	+	188.0	Naunyn.
Diabetic coma	+	+	+	100.0 to 150.0	Magnus-Levy

SOURCE OF ACETONE BODIES.

While, on theoretical grounds, it is quite possible that the acetone bodies may be derived from proteids, from carbohydrates,