Primary malignant disease of the vermiform appendix.

PRIMARY MALIGNANT DISEASE OF THE VERMIFORM APPENDIX

BY

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Primary malignant disease of the vermiform appendix has long been recognized, but the earlier reports of its occurrence are not sufficiently conclusive to warrant their acceptance as genuine, either from a lack of any histological confirmation or from absence of anatomical proof that the growth in the appendix was not secondary.

In reviewing the literature we have considered all cases of primary malignant disease of the vermiform appendix, whether described as carcinoma, endothelioma, or sarcoma.

Historical.

The earliest report of a case was Merling's (1) in 1838, in which an appendix found at an autopsy was thickened

and firm, with several small, hard tumours in its walls and a perforation near the base. He concluded that it was affected with primary malignant disease; but since microscopical evidence was, of necessity, wanting the case must remain doubtful. Twenty-seven years later, in 1865, Prus (2) described an appendix almost identical with that found by Merling, with the addition of a soft, sessile, hæmorrhagic tumour about the perforation, but this case, again, cannot rank owing to absence of any histological examination. For the same reason the four cases published by Rokitansky (3) in 1867 as instances of primary carcinoma must be excluded. These four patients died from other causes, and at the autopsies the appendix, in every case, was transformed into a cyst-like swelling, with fibrous walls and gelatinous contents, traversed by a delicate fibrous network. These were assumed to be examples of a stenosing colloid carcinoma, but, as suggested by Elling (4) and others, their characters are quite compatible with the view that the condition was one of cystic dilatation or mucocele of the vermiform appendix. A similar reticulated condition of the walls was met with in an appendix described by Latham (5) in which there was no suspicion of new growth. An interesting feature of these four cases is that the ages of the patients averaged 65, an age, as will be seen, that is more than double the average in the accepted cases (*vide* p. 8). The next reputed instance of primary carcinoma is Kolaczek's (6) in 1875, in which an abscess was opened in the right iliac fossa and never healed. At the autopsy there was carcinoma of the cæcum communicating with the fistula; the base of the appendix opened at the site of the ulcerated cæcum. There is thus no reason for the assumption that the carcinoma was other than primary in the cæcum. Leichenstein (7) in 1876, among 154 cases of primary carcinoma of the intestine, excluding those of the rectum, mentioned three involving the vermiform appendix, but, as he states that it is "a collection of published cases together with the records of pathological institutes and hospitals,"

there is no proof that they are original, and, furthermore, no details are given of their microscopical appearances. In 1880 Bierhoff (8) reported a case of carcinoma of the uterus, ovary, and rectum, with metastases in the liver and spleen and also a small nodule of new growth in the wall of the appendix, obstructing its lumen and producing a distal mucoid dilatation. There is no reason for supposing the change in the vermiform appendix to be other than secondary.

Up to this time, then, no reliable proof had been forthcoming as to the existence of primary carcinoma of the vermiform appendix, but in 1882 Beger (9) brought forward the first incontestable example in a man aged 47 years, who for three and a half years had suffered from a fistula in the right iliac fossa, dating from an abscess in that situation. At an operation the fistula was found to lead directly into the appendix, which was infiltrated throughout by carcinoma, the growth projecting into the cavity of the cæcum but not actually involving its walls. The patient died thirty-six hours after the operation, and post mortem the retroperitoneal glands were found to have become implicated, but there was no suggestion that the growth was other than primary.

Maydl (10) in 1883 mentions, without giving details, 1 case among 20,480 autopsies at Vienna; this is the same case as those sometimes attributed to Nothnagel (11) and Ziemann (12); so that these three reputed instances should, therefore, only rank as one case.

In the next case, reported in 1884 (13) by Draper, the ileo-cæcal valve was constricted and the gut above distended with fæces, the cæcum was thickened and red, while the appendix at one point was dilated and its walls showed the appearances characteristic of colloid carcinoma. Though this is possibly a genuine example of the disease under consideration, the change noted at the ileo-cæcal valve might be the primary growth, and the starting-point is not sufficiently certain to warrant admission to the list of cases.

In 1893 Hastings Gilford (14) reported a case of sarcoma of the appendix, basing his diagnosis upon the microscopical changes present; these, however, so closely resemble those of inflammation as to make the real nature of the disease still in doubt. Until this time, then, out of 14 reputed cases, all, with the exception of Beger's, are of too doubtful a character to be accepted.

From the year 1895, the date of Glazebrook's report of a case of endothelial sarcoma (15), verified by the microscope, and of Lockwood and Kanthack's psammoma, which is not included, as no details appear to have been published (16), we have reference to 48 reported examples of primary malignant disease, 5 of which cannot, for various reasons, be accepted, and 2 of which are the same as Maydl's case, already mentioned above (Ziemann, Nothnagel).

In the following year, 1896, Stimson (17) operated upon a patient the subject of a primary malignant growth, and in 1897 4 cases were reported, 1 by Mossé and Daunic (18), 2 among the 12 examples of obliterating appendicitis described by Letulle and Weinberg (19), and 1 by Ruyter (20), which must be referred to in some detail. The patient was operated upon for recurrent appendicitis; there were many adhesions around the appendix, which contained a concretion and was surrounded by numerous abscesses. Recovery after a protracted convalescence finally appeared to be complete, but six years later, when the man died from other causes, a small cystic tumour was found in the stump of the appendix, and proved microscopically to be carcinomatous. If the appendix was completely removed at the operation, any subsequent growth should be regarded as cæcal rather than appendicular in origin. Of course, if part of the adherent appendix was left behind as a stump, the growth may have been primary there, but in the absence of any statement to this effect it is unsafe to include the case in our present list.

The first recorded case of round-celled sarcoma was Warren's (21), in 1898, in which year J. H. Wright (22)

reported an instance of carcinoma. Monks (23), in 1899, published an example of a carcinoma involving the cæcum, in the centre of which was a slough, thought to be the remains of the vermiform appendix. Elting states that this case has sometimes been regarded as a primary growth of the appendix; this is certainly an erroneous view, and does not appear to have been held by Monks.

From 1900 reports of primary malignant disease become much more frequent, and nearly all can be accepted without question. In this year 2 more examples were brought forward by Letulle and Weinberg (24), another by Rolleston (25), a fourth by Giscard (26), a fifth by Hurdon (27), and 4 by A. O. J. Kelly (28), 1 of Kelly's being an endothelioma. In 1900 alone 9 genuine examples of primary malignant disease of the appendix were recorded, or as many as the total number of accepted cases before this year.

In Whipham's (29) case, published in 1901, a small growth of spheroidal-celled carcinoma was found post mortem in the vermiform appendix. This case, however, is excluded by several authors on the ground that there were growths also in the glands, liver, and the left ovary, which last they regard as the primary seat of the disease. It is, however, accepted by Moschcowitz (30), who agrees with Whipham that the origin in the mucous coat of the appendix shows that the growth was primary there, a view which we also take (*vide* p. 12). In this year a case of carcinoma was reported by McBurney (31), who mentioned another case of Lartigan's (the pathological nature of both having been recognised by Hodenpyl), and a fourth case was put on record by Goffe (32).

Jessup (33) in 1902 recorded one, and Harte and Willson (34) two other cases of undoubted primary carcinoma.

In the 'Annals of Surgery' for 1903 there were articles by Elting (4) and by Moschowitz (30), who discussed the subject at far greater length than had been attempted hitherto, and added 3 fresh cases each. We are indebted to these authors for the details of several cases which are not available in the originals.

In St. Bartholomew's Hospital 'Reports' for 1903 (35) one case of columnar-celled carcinoma of the vermiform appendix is mentioned without much detail; in the same year Weir (36) and Norris (37) each furnished a case, and Paterson (38) reported another example of sarcoma.

In 1904 there were 2 more examples of carcinoma recorded by Burnam (39), and by Fiske-Jones and Simmonds (40).

In 1905 1 case of carcinoma was recorded by Battle (41), and 1 of endothelioma by Sargent (42); and in their work on diseases of the vermiform appendix, Kelly and Hurdon (43) bring forward 3 fresh cases of carcinoma, and mention one of sarcoma by Bernays. This last, however, was sufficiently extensive to involve the apex of the cæcum, necessitating removal of that viscus, so that a cæcal origin for the growth is not outside the range of possibility.

This brings the literature on the subject up to the present date, and it will be seen that, after critically reviewing the reports of all the published cases, the number of satisfactory instances dwindles considerably.

Altogether, including a fresh one of our own, which we are reporting by the kind permission of Mr. H. S. Pendlebury, under whose care it was, there are 62 cases, which have, from time to time, been taken to be examples of primary malignant disease of the vermiform appendix, but out of these it is hardly fair, in the absence of microscopical evidence, to accept those of Merling, Prus, Rokitansky, and Maydl, and, by subtracting these 7 cases, the number is reduced to 55. The exclusion of Leichenstein's 3 cases, and of those attributed to Nothnagel and Ziemann, brings the number down to 50. Further, the cases of Kolaczek, Bierhoff, Draper, and Monks were probably primary in the cæcum, and in two others—Ruyter's and Bernay's—the growth was so situated as to involve the apex of the cæcum and to make that viscus appear to be the probable origin of the disease. Gilford's case and that recorded by Kanthack and Lockwood are not included for

reasons already given. Thus the total number of cases of primary malignant disease of the vermiform appendix which are available for analysis is reduced to 42.

Of these, 37 have been recorded as instances of carcinoma in one form or another by the following authors: Beger 1, Stimson 1, Letulle and Weinberg 4, Rolleston 1, Giscard 1, A. O. J. Kelly 3, Hurdon 1, McBurney 1, Lartigan 1, Mossé and Daunic 1, Wright 1, Whipham 1, Goffe 1, Jessup 1, Harte and Willson 2, Elting 3, Moschcowitz 3, Walsham 1, Weir 1, Fiske-Jones and Simmonds 1, Battle 1, Kelly, H., and Hurdon 3, Burnam 1, Norris 1, Rolleston and Jones 1; 3 have been reported as endothelioma—Kelly, A. O. J. 1, Sargent 1, Glazebrook 1; and 2 as sarcoma—Warren 1, Paterson 1.

It is interesting to note that out of our list of 42 cases no less than 28 are reported by American authors; of the remainder 7 are English, 6 French, and 1 German.

In most of these the condition was found during operation, but 8 of the carcinomas were found either at autopsies or as the result of routine examination of the appendix afterwards, and 1 endothelial sarcoma was so discovered. Such were the cases of Whipham, Letulle, and Weinberg (Cases 5, 6, 9, *vide* list of cases, p. 20), Mossé, and Daunic, Elting (Case 28), Wright, Lartigan, and Glazebrook.

There are, therefore, 33 instances in which primary malignant disease was found in appendices removed during life, but the true nature of the disease was not suspected in any case before operation.

As to the frequency of malignant disease in this situation, that it is a rarity no one would venture to deny, but now with the routine microscopic examination of appendices in cases of supposed appendicitis the number of instances of the disease will, no doubt, continue to increase. The fact that its malignancy is so much less than that of most carcinomas suggests that it may often have been overlooked. And again, the growth, especially if superadded to an already existing stenosis, has frequently, as in the

cases of Letulle and Weinberg, been so small as only to be recognized by the microscope. Out of the available 42 cases, 41 have been placed on record during the past ten years, a striking proof of the value of a routine examination of all appendices removed during life, or found post mortem to present the slightest suspicious pathological change. At St. George's Hospital alone, 2 appendices during the last five years, which had been excised for supposed simple inflammation, presented this change, and another was found at an autopsy. For these reasons, and from the ability of some authors to report 2, 3, or even 4 examples occurring in their own experience, it is fair to conclude that the rarity of the condition, though undoubted, has been exaggerated.

Etiology.

The *age* is given in 36 cases out of the 42 cases of primary malignant disease; the youngest patients[1] were those of Sargent, and of Letulle and Weinberg (Case 10), aged 12, and there were others aged 14 and 15; at the other extreme was a man aged 81 (Elting, Case 28), and it is interesting to note that both in this and the next eldest (A. O. J. Kelly, Case 16, aged 63) the growth was columnar celled, an unusual type in the vermiform appendix (see histology, page 135).

The average age is found to be 30·6, 30·3, and 39 years in the carcinomas, endotheliomas, and sarcomas respectively, or, taking all three classes together 30·8. If the two oldest patients mentioned above are excluded, the average is reduced to 27·8 years.

It is interesting to compare the age-incidence of primary carcinoma in other parts of the intestine. In 41 cases of primary carcinoma of the duodenum the average age was 52 years (44); in 9 cases of primary carcinoma of the jejunum and ileum that we have collected it was 47·2 years, in 30

[1] In a paper recording three fresh cases Baldauf ('Albany Medical Annals,' December, 1905) describes primary carcinoma of the appendix in a girl aged 8 years.

cases of primary carcinoma of the cæcum 47·8 years, and in 100 cases of primary carcinoma of the remainder of the large intestine 49·34 years (45). It therefore appears that the average age-incidence of primary carcinoma of the vermiform appendix is seventeen years lower than in other parts of the intestine.

Further, the age-incidence varies in the different kinds of carcinoma of the vermiform appendix, being 52 years in the columnar-celled, 32 in the transitional forms, 24 in the spheroidal-celled, and 25·5 in those merely described as "carcinoma."

The early occurrence of carcinoma is well seen when the ages are arranged in decades, as in the subjoined table :

Years.	Carcinoma.	Sarcoma.	Endothelioma.
1—10	—	—	—
10—20	6	—	1
20—30	12	—	1
30—40	7	—	—
40—50	4	1	—
50—60	1	—	1
60—70	1	—	—
70—80	—	—	—
80—90	1	—	—

27 out of 36, or 75 per cent., occurring before 40.

Sex.—In the 36 cases in which the sex of the patient is mentioned the difference is not sufficiently marked in the two sexes to draw the conclusion that the disease is commoner among women, as it appeared to be at the time of Moschcowitz's paper in 1903 ; 16 have been found in men and 20 in women (both the sarcomas were in men) ; 2 endotheliomas were found in women and 1 in a man, and 18 out of 31 carcinomas were in women.

Associated Conditions.

Only an incomplete summary of the morbid conditions found in the appendix in the published cases of primary new growth is possible, as, in many cases, the observer's

attention has evidently been focussed on the existence of the growth to the exclusion of any other less striking or less important feature.

Acute inflammation was found in 13 cases.

Obliterating appendicitis was mentioned in 11, in 3 of which the growth was described as arising at the stricture, but it is possible that the stricture in some of the other 8 cases was due entirely to the growth, as it was stated to be in Giscard's case (26), in which there was pus in the distal portion of the appendix and an abscess in the right iliac fossa.

Catarrhal appendicitis (Norris), chronic appendicitis with ulceration (Walsham), and chronic inflammation (A. O. J. Kelly) are mentioned in 1 case each.

Adhesions were stated to be present in 15 cases.

In 2 cases, Beger and Elting (Case 30, *vide* List, p. 148), there was a fistula of three and a half years and six months duration respectively.

The growth may, as already pointed out, produce a stricture; further, by projecting into the lumen it may completely obliterate the lumen, even (as in Case 42) in microscopic sections.

A concretion was mentioned as being present in only three cases (Letulle and Weinberg [Case 10], Walsham, and Hurdon). This is a striking contrast to the frequent associations of calculi and primary carcinoma of the gall-bladder.

The average length of the normal appendix is about 8 or 9 cm. (Lockwood (46)). In the case of primary malignant disease the average length of the recorded cases was found to be 7·4 cm.

Secondary Growths.

In only 5 of the 42 cases, or 12 per cent., were secondary growths described as being present; in 3 cases (Fiske-Jones and Simmonds, Beger, and A. O. J. Kelly [Case 16]), the abdominal lymphatic glands were involved, in 2 cases (A. O. J. Kelly [Case 16] and Elting [Case 30]) there were

multiple growths on the peritoneum, and in Whipham's case there were growths in the liver and right ovary. In 2 out of the 5 cases the growth was a columnar-celled carcinoma (A. O. J. Kelly (Case 15) and Beger).

Whipham's case was the only one in which the metastatic growths were found at the autopsy; in the others the condition was seen during the course of operation.

The *situation of the growth* is given in 33 cases: The growth involved the whole length of the appendix in 4, it was situated at the tip in 7, near the tip in 9, in the middle in 4, at the middle and tip in 1, and near the base in 8.

Cases in which the growths involved the junction with the cæcum have not been included in our 42 cases, because, as already stated, it seemed necessary to avoid any possible inclusion of cases really primary in the cæcum. It is possible that some cases primary in the cæcal end of the appendix have thus been excluded. In the 33 cases here analysed at least 16, or 48 per cent., were growths localised in the distal third.

As already mentioned, the growths may occur at the site of stricture, and in Battle's case it occurred between two strictures.

The size of the growth varied from that of a pigeon's egg in Glazebrook's endothelial sarcoma to those of microscopical dimensions, as in Letulle and Weinberg's series. As a rule it was the size of a pea to that of a marble, nearly always white in appearance and firm in texture.

Microscopic Appearances.

Of the 42 cases of primary malignant disease of the vermiform appendix 37, or 88 per cent., were described as one form or another of carcinoma, 3 as endothelioma, and 2 as sarcoma.

From the tabular statement it is seen that of the 37 cases of primary carcinoma 17, or 45 per cent., appear from the descriptions given (*vide* Appendix, p. 144) to be polyhedral- or spheroidal-celled (1 being colloid), 6 cases as transitional

from the columnar-celled to the spheroidal-celled type, 6 columnar-celled carcinoma (1 being colloid), and that 8 cases are described merely as "carcinoma."

There are thus two distinct types of primary carcinoma of the vermiform appendix: (1) the columnar-celled, like that met with in the large intestine, and (2) the spheroidal-celled.

As already pointed out, the average age of the 5 cases of columnar-celled carcinoma of the vermiform appendix was 52 years, thus corresponding with the average age of primary carcinoma of other parts of the small and large intestines. The special character of spheroidal-celled carcinoma of the vermiform appendix is shown (*a*) by their benign nature (*vide* pp. 142, 143), (*b*) by the early age incidence, for the average age of the 14 available cases was only 24·2 years, the extremes being 37 and 12 years. Since the average age of the 6 of the 8 cases described merely as "carcinoma," in which the age is available, was 25·5 years, it is highly probable that many of them were examples of spheroidal-celled carcinoma. In this connection it is interesting to note that the average age of the 6 cases, showing a transition from columnar- to spheroidal-celled carcinoma was 32·7 years.

Some reference must be made to the histology of the spheroidal-celled type, as it differs so markedly from the columnar-celled carcinoma met with in the colon.

In Whipham's case, in which there were metastases causing death, the growth was an ordinary spheroidal-celled carcinoma of rapid growth arising in Lieberkühn's crypts. Our recent examination of the sections shows that the type of spheroidal-celled carcinoma is distinct from that about to be described; the cells of the growth are larger, and the alveoli do not show the vacuolation to be mentioned below. This is of significance in connection with the manifest malignancy of Whipham's case and the remarkable benignancy of the other type of spheroidal-celled carcinoma.

The following brief description applies to two specimens

(Cases 11 and 42) that we have examined at St. George's Hospital, and probably to many of the recorded spheroidal- or polyhedral-celled carcinomas.

The arrangement of the growth is alveolar, the cells occupying the alveoli are round and polyhedral, small, and somewhat resembling those of rodent ulcer. There is a scanty margin of clear protoplasm around the nuclei, which

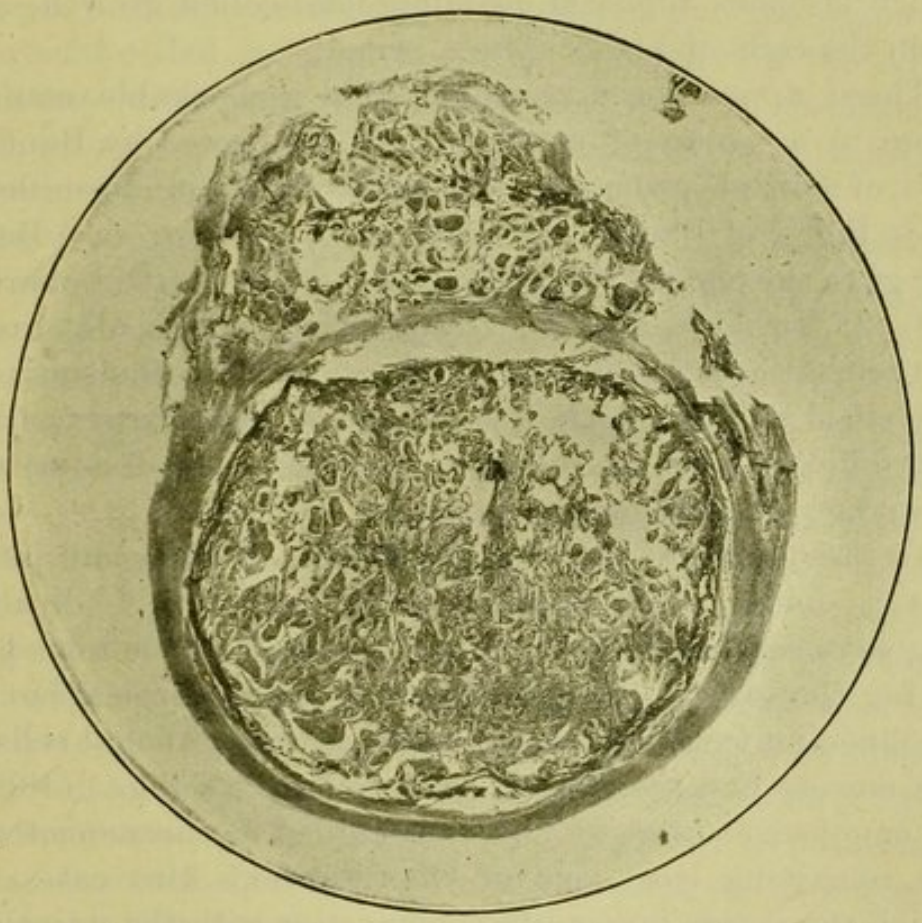

FIG. 1.—Section of primary spheroidal-celled carcinoma of the vermiform appendix (Case 42), showing growth filling up the lumen of the appendix and at one point infiltrating its wall. × 12. [Photomicrograph by Dr. H. R. Spitta.]

stain sharply and show nucleoli. The cells are in close contact and fill the alveoli, but in some alveoli there are one or more clear spaces, apparently due to degeneration of the surrounding cells. The spaces thus produced are more often empty, but may contain spindle-shaped cells like those forming the walls of the alveoli. This vacuolated appearence is a striking feature of the growth

(Fig. 1). The alveolar walls are delicate, and formed of spindle-shaped connective-tissue cells. It may be difficult to determine the starting-point of the tumour, but from an examination of sections from two cases at St. George's Hospital and one of Dr. Hurdon's (to whom we are much indebted for a slide sent by the courtesy of Dr. Bunting) we incline to the view that it is in the mucosa, which becomes replaced by spheroidal-celled growth, and from the cells of Lieberkühn's crypts.

These appearances resemble in a remarkable manner those in a group of cases, recently collected by Bunting (47), of multiple primary carcinomata of the jejunum or ileum (*vide* Fig. 2 of Plate). In addition to his own case Bunting gave the main points of five other examples (O. Lubarsch (48), 2, Notthaft, Walter, Oberndorfer), which all agreed in their structure and their benign character. Ransom (49) described and figured a case which had a similar structure, but differed from the others in the presence of numerous secondary growths in the liver.

In these multiple primary carcinomas of the small intestine a similar vacuolation of the alveoli, due to hyaline degeneration of the cells in the centre, was mentioned as giving the growth the appearance of a cylindroma, but as a connection could be traced between the epithelial cells of the mucosa and the growth (*vide* Lubarsch's Figs.) (48) in six out of seven cases they were regarded as carcinomatous; the remaining case (one of Oberndorfer's two cases) in which there was no manifest connection with the intestinal epithelium, was termed a "lymphatic endothelial carcinoma."

The histological nature of these multiple primary growths of the ileum and jejunum is evidently the same as in those spoken of as primary spheroidal-celled carcinoma of the vermiform appendix; further, the growths in both cases are nearly always benign, and in this respect, it is true, resemble some forms of endothelioma more than spheroidal-celled carcinoma.

Two closely allied forms of carcinoma of the skin, how-

ever, rodent ulcer and the basal-celled growths of Krompecher (50), of which fifteen cases of multiple growths of the scalp collected by Dubréuilh and Auchè (51) are examples, resemble the spheroidal-celled carcinomas of the small intestine and vermiform appendix both in structure and benignancy.

There is, however, an etiological difference between the multiple primary carcinoma of the ileum and the primary spheroidal-celled carcinoma of the appendix in the age-incidence, averaging 46·8 years in five of Bunting's cases, as compared with 24·2 years in the cases of primary spheroidal-celled carcinoma of the appendix.

The vacuolated appearance of the contents of the alveoli resembles that seen in some of the tumours regarded as endotheliomas, especially those of the parotid region and of the upper jaw. By the courtesy of Mr. Dudgeon we have had the opportunity of examining a section of the primary endothelioma removed by Mr. Sargent in which the appearances are so much like those just described as spheroidal-celled carcinoma that the difficult question of nomenclature arises, for it is obvious that what one observer terms endothelioma may be regarded by another as a carcinoma. Thus, from difficulty in determining the starting-point of what we have here spoken of as primary spheroidal-celled carcinoma, similar histological growths may in the future, as they have in at least one case in the past, be described as endothelioma. It would therefore be unsafe to insist on too sharp a distinction between the cases recorded as spheroidal-celled carcinoma of the vermiform appendix on the one hand and as endothelioma or sarcoma on the other hand.

Clinical Considerations.

From the cases available for analysis it would be useless to attempt to build up a clinical picture by which a diagnosis could be made; indeed, as has been already pointed out, the diagnosis has never been made before operation. This is hardly surprising, since the symptoms in nearly

every instance were those of appendicitis in one form or another.

The extension of the growth to the cæcum may mask its true origin if symptoms do not arise to call attention to it at an early stage. Kolaczek's case may have been of this nature; in one of Elting's cases (Case 30) the growth had spread, from its origin, far along the other viscera; the tumour was close to the cæcal apex in Fiske-Jones's and Simmonds's case, and in Bernay's case the fact of the cæcal apex being involved prevents its acceptance.

The past history of the patients.—In those cases in which the condition was found after death the growth was the cause of death in two only, namely in Wright's case from "peritonitis of obscure origin," and in Whipham's, which is remarkable in being the only one on record in which the growth proved directly fatal by its extension.

The reasons which led to the operation in the thirty-three patients from whom the appendix was removed during life were as follows:

Four of the operations, those of Hurdon, Jessup, Elting (Case 29, *vide* list), and Norris, were undertaken for the relief of symptoms referable to the female pelvic viscera, for retroversion of the uterus in Hurdon's case, and for salpingitis in the other three; in all these four the disease was wholly unsuspected before operation.

Beger's patient and one of Elting's (Case 30, *vide* list) underwent operation for the relief of a fistula dating from an iliac abscess that had refused to heal; in Elting's case this was thought to be due to tuberculous disease of the cæcum.

In the remaining twenty-seven the symptoms pointed to appendicitis in one form or another, and may be separated into four groups:

(*a*) Symptoms of the first acute attack, 10 cases.

(*b*) Chronic symptoms with an acute attack, 3 cases.

(*c*) Recurrent attacks, 9 cases.

(*d*) Chronic appendicitis, 5 cases.

In some, then, the condition appeared to be acute and of

short standing, while in others the symptoms had extended over many years, in one case twelve years.

Can these extremes be reconciled with the view that the growth is directly or indirectly the cause of the symptoms? Or must it be assumed that the growth is a mere accidental occurrence or the result of the real cause of the symptoms?

In the more acute cases it is easier to admit the possibility that the growth is the actual cause of the inflammatory trouble, for it may ulcerate and allow of infection of the walls of the appendix, it may block the lumen, or it may interfere with the nutrition of the tissues by compressing the blood-vessels.

In those cases, again, with long-standing symptoms, the obvious objection that the growth, if the primary cause, would long since have formed metastases, or have spread locally and caused the death of the patient, can be met in part by the fact that these tumours do not tend to form metastases.

On the other hand, Letulle and Weinberg and other authors have laid especial stress on the probability that chronic inflammatory change is the precursor of malignancy, just as carcinoma of the breast and stomach may be preceded by mastitis and gastric ulcer.

The growth, it appears, may be either the cause or the effect of the changes producing the symptoms, and may give rise to the symptoms of appendicitis; it is probably the cause in those cases with an apparently acute onset, or in which, the symptoms having been chronic, the growth is the main feature of the appendix.

It is probably the outcome of chronic irritation in those cases of obliterating appendicitis in which the growth is only recognised by the microscope.

The actual changes found to exist with the growth when a further examination is made have been dealt with under the Associated Conditions (*vide* p. 133).

The extent of the operation called for by the diseased appendix but rarely exceeded the simple removal of the appendix.

In three of the operations a portion of the cæcum surrounding the base of the appendix was excised with the latter organ (Fiske-Jones and Simmonds, Paterson, Kelly and Hurdon, Case 39). In one case (Fiske-Jones and Simmonds) it was necessary to remove some glands in the mesentery.

Beger operated for the relief of a persistent iliac fistula. Elting, operating for a similar condition, was forced to remove the cæcum and part of the colon and ileum owing to the wide spread of the disease (Case 30), and the sarcoma in Warren's case was so extensive as to require a similar operation.

The results, immediate and remote, of the operation, have been surprisingly good.

There were four deaths within two weeks of the operation. Beger's patient, who had had a fistula in the iliac region for three and a half years, did not survive the attempt to remove the condition.

One case of Elting (Case 30), also with a fistula, in whom the operation consisted in the removal of a large amount of intestine, died two weeks later; one case (A. O. J. Kelly [Case 16, *vide* p. 145]), a man of 63, in whom the growth had formed secondary metastases, also died; and the fourth patient was Paterson's, in whom it was necessary to remove part of the cæcum.

In the majority of the other cases recovery is definitely stated to have occurred.

The presence of the growth, unless it is so advanced as to require removal of some additional portion of the intestinal tract, seems not to increase the risk of the operation of appendicectomy. Of the twenty-nine patients who made recoveries, one died four months later (Harte and Wilson, Case 24) after an operation to relieve obstruction caused by a band in the right iliac fossa, but post mortem there was no recurrence.

None of the other patients—and some have been heard of years after the operation—can be found to present any suggestion of recurrence.

A case recorded by one of us (24) was at the time of the original report suffering from symptoms compatible with the view that a recurrence had occurred, and is mentioned by Howard Kelly and Hurdon in their monograph on 'Diseases of the Vermiform Appendix' as the only case in which recurrence was thought to have occurred. We are indebted to Mr. H. M. Ramsay for the information that she was in perfect health in July, 1905.

This is striking evidence of the slight malignancy of these growths compared with those in nearly all the other parts of the alimentary canal.

Conclusions.

(1) The disease is one which renders an accurate diagnosis impossible; every case in which the symptoms drew attention to this region exactly imitated appendicitis in some form.

(2) Most of the older reputed examples fail to withstand investigation; but as 80·9 per cent. of the 42 genuine examples have been reported since 1900, the disease cannot be quite so rare as has been thought. The microscopic size of the growth in some cases makes it probable that many such instances have been overlooked.

(3) Pathologically, several varieties of carcinoma have been reported, and also sarcoma and endothelioma. The growth is usually, however, a spheroidal-celled carcinoma which is peculiar in the early age-incidence, the slight malignancy, and the resemblance to endothelioma. Colloid change is not common, as has been hitherto supposed.

(4) The presence of concretions is only mentioned in 3 cases out of 42.

(5) The disease is not prone to affect one sex more than the other.

(6) Inflammatory changes, either chronic or acute, very frequently accompany the growth.

(7) The immediate prognosis and the prospect of freedom from subsequent recurrence after operation are very good, particularly in the spheroidal-celled carcinomas.

Appendix.

Forty-two Cases of Primary Malignant Disease of the Vermiform Appendix.

1882: (1) Beger ('Berlin. klin. Wochens.,' 1882, xix, 616).—Male, aged 47, three and a half years before developed an abscess in right iliac fossa; incision; pus evacuated; wound refused to heal. Operation: fistula found to lead direct into appendix which was infiltrated throughout by carcinoma. Death soon after. Post mortem: Glands found affected; no other growth.

1895: (2) Glazebrook ('Virgin. med. Monthly,' vol. xxii, p. 221. Quoted by Elting).—Male, aged 55, died of cerebral hæmorrhage; growth, the size of a pigeon's egg, found at post-mortem in appendix; many adhesions; appendix normal for proximal three inches; tumour hard and fibrous; walls of viscus infiltrated with nests of irregularly cuboidal and cylindrical cells, reported as endothelial sarcoma.

1896: (3) Stimson ('Annals of Surgery,' vol. xxiii, p. 186).—Female, aged 44. Acute appendicitis ten years before, another attack one month before, a severe attack in which operation was performed; appendix 4 inches long and 1 inch thick, much thickened mucosa (projecting as a ring). Carcinoma.

1897: (4) Mosse et Daunic ('Bull. Soc. Anat.,' Paris, 1897, p. 814).—Female, aged 50. Found at post-mortem; death from heart disease. Diffuse growth; appendix 4 cm. long, 1·5 cm. thick; in parts growth was of cylindrical cells, while in parts it presented more of an alveolar arrangement. Lumen almost obliterated.

(5, 6) Letulle et Weinberg ('Bull. Soc. Anat.,' Paris, 1897, p. 747).—Mentioned in a report on 12 cases of obliterating appendicitis, among which 2 cases had developed carcinoma at the site of stricture.

1898: (7) Warren ('Boston Med. and Surg. Journ.,' vol. cxxxviii, p. 177, 1898).—Young male. Symptoms of chronic appendicitis for one month, recently with a definite swell-

ing. Operation: Appendix the site of round-celled sarcoma, spreading to mesentery; removal of cæcum; anastomosis by Murphy's button.

(8) Wright, J. H. ('Boston Med. and Surg. Journ.,' vol. cxxxviii, p. 150, 1898).—Found at post-mortem of a case of general purulent appendicitis of obscure origin, slight adhesions around, but no actual perforation. There was a small primary adeno-carcinoma at the tip.

1900: (9) Letulle et Weinberg ('Bull. Soc. Anat.,' Paris, 1900, p. 374).—Found post-mortem. Appendix hard and obliterated in its lower quarter, end of appendix practically a mass of carcinoma, with very small cells.

(10) Ibid.—Child, aged 12. Acute appendicitis, August, 1897, leaving some tenderness in right iliac fossa; another attack in January, 1898, with a definite cæcal mass; recovery in ten days, leaving appendix thick and palpable; another slight attack on March 1st. Operation March 28th. Appendix 4 cm. long, adherent, containing pus and a concretion; definite stenosis, found to be carcinomatous with very small cells, infiltrating meso-appendix; tip, beyond, dilated, showing ulceration and chronic changes.

1900: (11) Rolleston ('Lancet,' 1900, vol. ii, p. 11).—Woman, aged 26. Fourth attack of appendicitis, formal amputation on day after admission, adhesions, no glands. Caseous-looking swelling, about the size of a marble, found to be spheroidal-celled carcinoma. Alive and well July, 1905.

(12) Giscard ('Toulouse Imp. St. Cyprien,' 1900, 360, p. 51. Quoted by Elting).—Male, aged 37. First attack mild, two and a half years before, second attack severe, abscess opened in right iliac fossa, appendix found obstructed about centre by what appeared to be a cicatrix, found to be new growth between mucosa and muscle; superficially adeno-carcinoma; deeper, an alveolar arrangement.

(13) Kelly, A. O. J. ('Proc. Path. Soc. Philadelphia,' 1900, p. 109).—Full details not known. A case of acute gangrenous appendicitis. At distal end polyhedral-celled carcinoma.

(14) Ibid.—Woman, aged 24. Attack of diffuse abdominal pain, with vomiting, one year ago; since then three other attacks; last attack three weeks before, when pain became localized to right iliac fossa. Appendix easily felt and found free from adhesions; 9 cm. long, 5 cm. thick; ordinary changes of appendicitis, and also endothelioma near base.

(15) Ibid.—Male, aged 19. Eight days before operation all signs of ordinary acute appendicitis, with definite swelling. Small localized abscess found. Appendix 5 cm. long and 1 cm. thick. Chronic changes and small carcinoma near base.

(16) Ibid.—Male, aged 63. Recently many attacks of acute pain and vomiting; signs of appendicitis. Appendix very adherent; numerous small "tubercles" on peritoneum and intestine. Glands enlarged. Death. Appendix 2 cm. long, 1·2 cm. thick. Firm and nodular, infiltrated throughout by growth of cylindrical and polyhedral cells; lumen obliterated in distal third.

(17) Hurdon ('Johns Hopkins Hosp. Bull.,' vol. xi, p. 175).—Woman, aged 24. Symptoms of uterine trouble from birth of child eight years before. Pain and vomiting for eight months, ascribed to movable kidney. Operation on uterine condition; retroflexion found; also appendix adherent and kinked, distended at tip by concretion; also an oval tumour 10 by 5 mm., proving to be adeno-carcinoma, involving all the coats.

1901: (18) Whipham, T. R. ('Lancet,' 1901, vol. i, p. 320).—Woman, aged 45. History of loss of flesh for six weeks and a swelling for fourteen days; thought to be malignant and inoperable. Post mortem, spheroidal-celled carcinoma at base of appendix, with secondary growths in liver, glands, and ovary.

(19) McBurney ('Med. Record,' N.Y., vol. lx, p. 478).—Female, aged 23. Clear attack of appendicitis two years before, leaving some pain in right iliac fossa. Symptoms more severe for two months. Appendix 4 in. long, not adherent. Two strictures, and near the tip a small, white,

firm tumour, the size of a pea. Microscopically, carcinoma.

(20) Lartigan.—Male, aged 30. Mentioned without details by McBurney.

(21) Goffe ('Med. Record,' N. Y., vol. lx, p. 14).—Female, aged 15. For more than a year steadily increasing pain in right iliac fossa. Diagnosis of chronic appendicitis. Appendix unusually long, thick, and tortuous; smooth, round, white body, the size of a pea, in extreme tip; on section, like fibrous tissue; by microscope, typical carcinoma.

1902: (22) Jessup ('Med. Record,' N. Y., vol. lxii, p. 289).—Woman, aged 36. History of pain in right iliac region since an abortion. Operation on uterine appendages. Appendix found firmly bound down by adhesions; bent at an angle, and beyond this a dilatation occupied by a firm, white tumour; adeno-carcinoma, polygonal, and cylindrical cells, with alveolar arrangement.

(23) Harte and Willson ('Trans. Amer. Med. Assoc.', vol. xx, p. 228).—Female, aged 24. Five years ago, supposed acute appendicitis; one year ago a recurrence, one month ago another attack, with formation of a lump; appendicectomy; organ 15 cm. long, no adhesions, constriction, or obvious growth. Most of lumen obliterated, central part necrotic, and small area of spheroidal-celled carcinoma.

(24) Ibid.—Male, aged 25. Eight months before pain in right iliac fossa, when seen an acute appendicitis diagnosed; appendix found perforated, showing cubical-celled carcinoma beginning near tip; four months later admitted with obstruction by fibrous band near cæcum. Operation; death; post mortem, no recurrence of growth.

1903: (25) Moschcowitz ('Annals of Surgery,' vol. xxxvii, p. 891, 1903).—Male, aged 37. Symptoms supposed to be due to gastritis for eight months. For one day symptoms of acute appendicitis, with a mass in right iliac fossa. Operation, an abscess, appendix adherent; spheroidal-celled carcinoma near base, and acute changes.

(26) Ibid.—Female, aged 20. Onset of pain in right iliac fossa ten days before without vomiting or fever; tenderness in right iliac fossa, no swelling; appendix removed, found adherent, with signs of acute inflammation and spheroidal-celled carcinoma beginning near tip.

(27) Ibid.—Female, aged 24. Five days before being seen pain in hypogastrium, rigor; temperature 105°. No definite symptoms, but after two days condition so bad that abdomen was opened and appendix found three inches long with a thickened, obliterated, distal portion, which proved to be the site of a carcinoma of transitional type.

(28) Elting ('Annals of Surgery,' vol. xxxvii, p. 549, 1903).—Male, aged 81. Found post mortem; death from cardiac disease; appendix 5½ cm. long, proximal 2 cm. normal. Distal, 3½ cm., swollen and filled with gelatinous contents, which in one place had fungated through the coats. Colloid carcinoma.

(29) Ibid.—Female, aged 36. Attack of pelvic peritonitis eight years before. Recently return of symptoms, double salpingo-oöphorectomy performed and appendix also removed. Appendix 4 cm. long, about 1 cm. from distal end, a slight bulging, obliterating the lumen; author finds it difficult to say whether growth was an alveolar spheroidal-celled carcinoma or an endothelioma.

(30) Ibid.—Male, aged 19. An attack of acute appendicitis, abscess opened and drained; six months later sinus had not healed but discharge was not fæcal. Diagnosed as tubercle of the cæcum. At operation mass in right iliac fossa, found to be new growth, involving appendix, cæcum, ileum, and colon—considered primary in appendix; spheroidal cells.

(31) Walsham, W. J. ('St. Bart's. Hosp. Reports,' vol. xxxix, Surgical Registrar's Report).—Male, aged 45. Several attacks of appendicitis; appendix thickened and ulcerated; microscopically columnar-celled carcinoma with alveolar arrangement. Concretion present.

(32) Weir ('Med. Record,' N. Y., 1903).—Male, aged 23. Thirteen apparent attacks of appendicitis in two years.

Nothing felt *per abdomen*. Operation; clubbed, thickened appendix which showed the usual inflammatory changes and an adeno-carcinoma at the tip.

(33) Norris ('Univ. Penn. Med. Bull.,' 1903, p. 334).—Female, aged 27. Operation on right Fallopian tube for symptoms of two years' standing. Appendix found, thickened and inflamed, 7·5 cm. long, adhesions present; for 1·5 c.m. from the tip the lumen was occluded by friable mass of growth; "although the nests are almost solid plugs, yet vacant areas occur around which the cells are arranged with some regularity."

(34) Paterson, P. ('Practitioner,' 1903, vol. lxx, p. 515. Male, aged 39. Uneasiness in right iliac fossa for three months; four attacks of definite pain; when seen, symptoms of subacute appendicitis. Thickened, firm, adherent appendix removed with portion of cæcum. Death. Post mortem, no trace of sarcoma elsewhere. Appendix 16·5 cm. long, 10 cm. round; very thick walls; much ulceration; round-celled sarcoma, infiltrating all coats except peritoneal.

1904: (35) Fiske-Jones and Simmonds ('Boston Med. and Surg. Journ.,' vol. cli, p. 566, 1904).—Female, aged 26. Four attacks of "colic," first attack twelve years ago, the last three months before. No swelling felt. At operation thickened area at base, through which appendix was ligated; area found to be spheroidal-celled carcinoma; second operation to remove stump and portion of cæcum.

(36) Burnam ('Johns Hopkins Hosp. Bull.,' vol. xv, p. 136, 1904).—Male, aged 25. Recurrent attacks of pain in right iliac fossa; one attack subsiding at time of operation. Appendix found adherent, 6 cm. long, 75 cm. thick at base; cæcal end normal, outer two-thirds inflamed; at the tip a yellow core of growth, filling up lumen and replacing mucosa and sub-mucosa, cells arranged in small alveoli. Adeno-carcinoma.

1905: (37) Battle ('Lancet,' 1905, vol. i, p. 291).—Female, aged 14. Symptoms of appendicitis on four occasions; some fulness in right iliac fossa; nothing else

abnormal. Appendix 2 inches long; fibrinous exudate; congested thick walls, two constrictions, between which a marble-like structure, proved to be spheroidal-celled carcinoma.

(38) SARGENT ('Lancet,' 1905, vol. ii, p. 889).—Female, aged 12. First attack; three weeks' history; small mass to be felt. Appendix 3 inches long, acutely inflamed, deeply ulcerated but not perforated; obstruction ½ inch from cæcum by small mass, size of a pea. Reported as endothelioma.

(39) H. KELLY and HURDON ('Diseases of the Vermiform Appendix,' 1905).—Female, aged 30. Recurrent appendicitis for seven years; pain becoming severe; operation in quiescent period. Appendix much thickened, distal portion cystic, base being indurated, removed with V-shaped portion of cæcum. Examination showed case to be affected with columnar-celled carcinoma with alveolar arrangement.

(40) IBID.—Woman, aged 24. Two days' history of pain without other symptoms; previous history of indigestion. Appendix found adherent, with a bulbous tip; small nodule near tip, 6 inches in diameter. "Carcinoma."

(41) IBID.—Male, aged 19. Recurrent attacks of cramp, but no definite attack of appendicitis until ten days before admission, when mass was felt in right iliac fossa. Appendix densely adherent, with small abscess, 8 cm. long, central 2 cm., thick and dense. Microscopically small alveoli packed with cells.

(42) ROLLESTON AND JONES.—Female, aged 31. Six days' history of abdominal pain, with vomiting and distension. No previous attack. Cæcum found much distended; clear fluid in pelvis; appendix slightly swollen at tip, not adherent; at the tip a small, white, firm mass, proved to be spheroidal-celled carcinoma (case not previously reported).

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To Dr. Harold Spitta our sincere thanks are due for the photomicrographs illustrating this paper.

DISCUSSION

Mr. W. McAdam Eccles reported the following Case of Primary Carcinoma of the Vermiform Appendix:

I was asked on May 17th, 1904, by Dr. S. Verdon-Roe, to see a young gentleman, aged eighteen, with the following history:

He had had one or two slight attacks of pain in the right iliac fossa during 1903, but was never confined to bed or even to the house by them.

On April 6th, 1904, a more pronounced attack of pain supervened, and there was much tenderness in the appendix region. He was seen by Dr. Verdon-Roe, who found the temperature raised to 100° F., and a definite swelling in the right iliac fossa. He was kept in bed for fourteen days, then allowed up, and shortly afterwards went to Hastings.

A second sharp attack of pain occurred on May 12th, 1904. Again the temperature was somewhat above the normal, and there was distinct induration in the right iliac fossa. He remained in bed, and no evidence of suppuration appeared, though the swelling persisted.

When seen on May 17th, his temperature and pulse were normal; all the pain had gone, but there was marked tenderness in the right iliac fossa, and an easily palpable, hard, resistant mass was present.

As no symptoms indicating the necessity for an immediate operation existed, it was agreed to defer laparotomy until May 25th, 1904. On that day a "split-muscle" opening was made over the mass, exposing the cæcum fixed by adhesions in the fossa, and behind it a hard mass which was clearly a diseased appendix.

With some difficulty this was separated from the adhesions around and found to be an appendix one and three quarter inches long, pointing upwards and outwards behind the cæcum. It was greatly thickened, having an external circumference of two and a quarter inches.

One or two lymphatic glands were removed from the base of the appendicular mesentery, but unfortunately these were not preserved for examination.

The wound was closed in the usual manner, and the patient made an uninterrupted recovery. When seen on February 19th, 1906, he was perfectly free from any recurrence and quite well in health.

When the appendix was cut through longitudinally there were two whitish patches in its walls, one at a spot about one

third its length from its cæcal attachment, and the other a little more distal. These two patches were absolutely distinct from one another. They were taken to be probably of the nature of tuberculous deposits. There were no concretions within the lumen of the appendix. On microscopical examination, however, both the deposits proved to be spheroidal-celled carcinoma.

This case is another example of an undoubted carcinoma of the appendix, primary in origin, and occuring in a male of only eighteen years of age. It is also of interest in that two separate foci of carcinoma existed. It was impossible to diagnose their existence before operation, the signs and symptoms being only those of a chronic appendicitis.

It is satisfactory to note that the patient is in perfect health now, twenty-one months after the removal of the diseased organ.

The PRESIDENT said that the cases were etiologically interesting, especially with regard to the question whether the cancer was primary or secondary to inflammatory changes. The duration was remarkable. The diagnosis was, apparently, of academic interest only, since the treatment by removal was uniform with that of simpler inflammatory varieties of the disease with which it was usually confused, and, so far as experience as yet went, with equally good results. Subsequent histories of these cases would, however, be of interest to the Society, and he hoped that the authors would supply them.

Mr. T. JEFFERSON FAULDER quoted the case of a patient who had three attacks of apparent appendicitis. In 1902 the appendix was removed, and was found to be infiltrated with columnar-celled carcinoma undergoing spheroidal-celled transformation. The appendix contained some concretions. The patient made a good recovery, and was now, four years after the operation, in good health. Columnar-celled carcinoma undergoing spheroidal-celled transformation was, when it occurred elsewhere in the intestinal tract, regarded as actively malignant, whereas when in the appendix the growth did not seem to possess any great malignancy. He suggested that all such growths should be regarded as endothelioma.

Dr. NEWTON PITT said that another class of malignant growths, namely lymphadenomata, might start in the appendix. It was a point of interest whether there was any evidence of local infection when there were multiple nodules in the appendix, and whether the growths were opposite or close to one another. He remarked on the small size of the cells in these appendix tumours which thus markedly differ from those in the stomach. Were the central spaces empty alveoli with fibrous-tissue walls, or were they the result of central degeneration in the masses of cells ?

Dr. HERBERT FRENCH remarked on the small size of the growths. It would have been anticipated that so cellular a

tumour would have grown to a large size if carcinomatous. How could inflamed lymphatic tissue be differentiated from the growths? What were the microscopic characters of the tumours from which there were metastases as compared with those from which there were none?

Dr. ROLLESTON, in reply, said that he had been much interested in Mr. Eccles' case, and that it was interesting to note that the white appearance of the growth had suggested caseous tubercle, both in Mr. Eccles' case and in that reported by himself in the 'Lancet' in 1901. Mr. Eccles' case was also remarkable in the presence of two distinct growths, and these resembled Bunting's primary multiple carcinomata of the ileum. The question of the nomenclature of these tumours had been discussed in the paper, and the reasons why the tumours were regarded as belonging to the group of the carcinoma rather than to that of endothelioma had been stated. The tendency to apply the term "endothelioma" to any tumour merely because the appearances presented were anomalous was undesirable. In reply to Dr. French's question whether there was any known example of such a richly cellular tumour with slow growth and low malignancy, it was only necessary to point to rodent ulcer. The suggestion made that the appearances were due to inflammation of lymphoid tissue was not compatible with the histological appearances, which were also quite unlike those of lymphadenoma. The spindle-cells inside some of the vacuoles he regarded as portions of the alveolar walls cut transversely. The multiplicity of the growths in Bunting's case of multiple primary carcinomata of the ileum and jejunum could not be explained by supposing that local infection had taken place from a single primary growth.

Mr. ECCLES added that there was nothing in his case to suggest infection from one focus to the other by contact. The nodules were separate and quite distinct; they were on the same side of the appendix, and one was considerably below the other.

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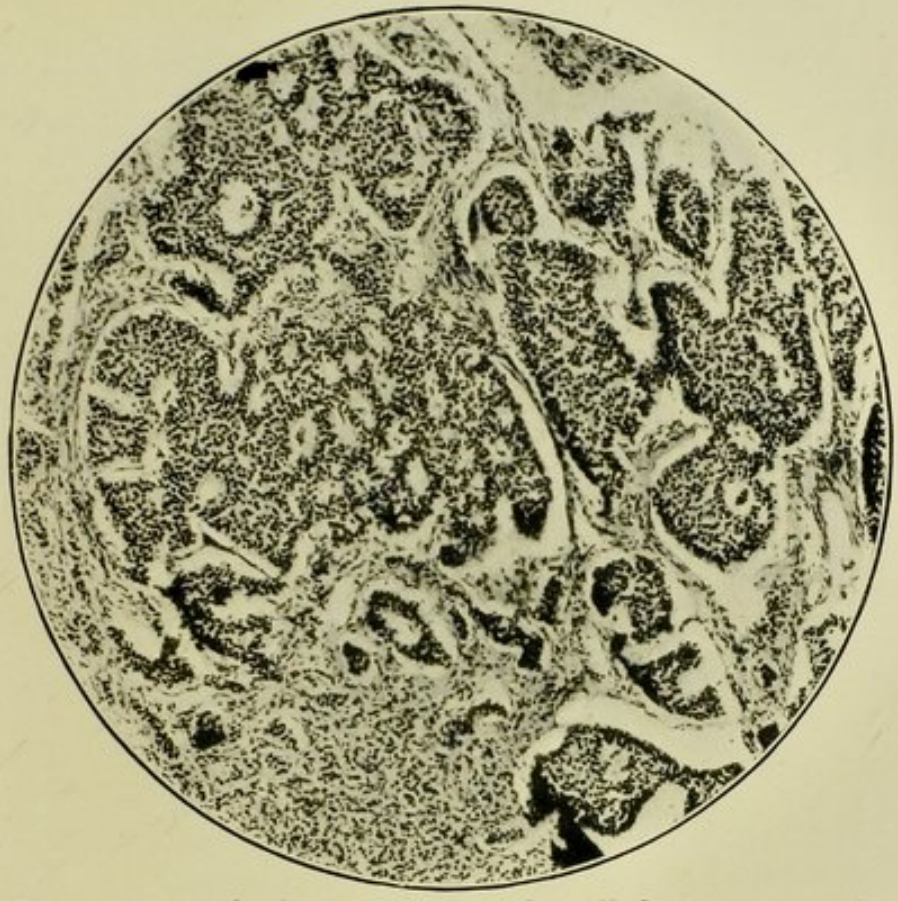
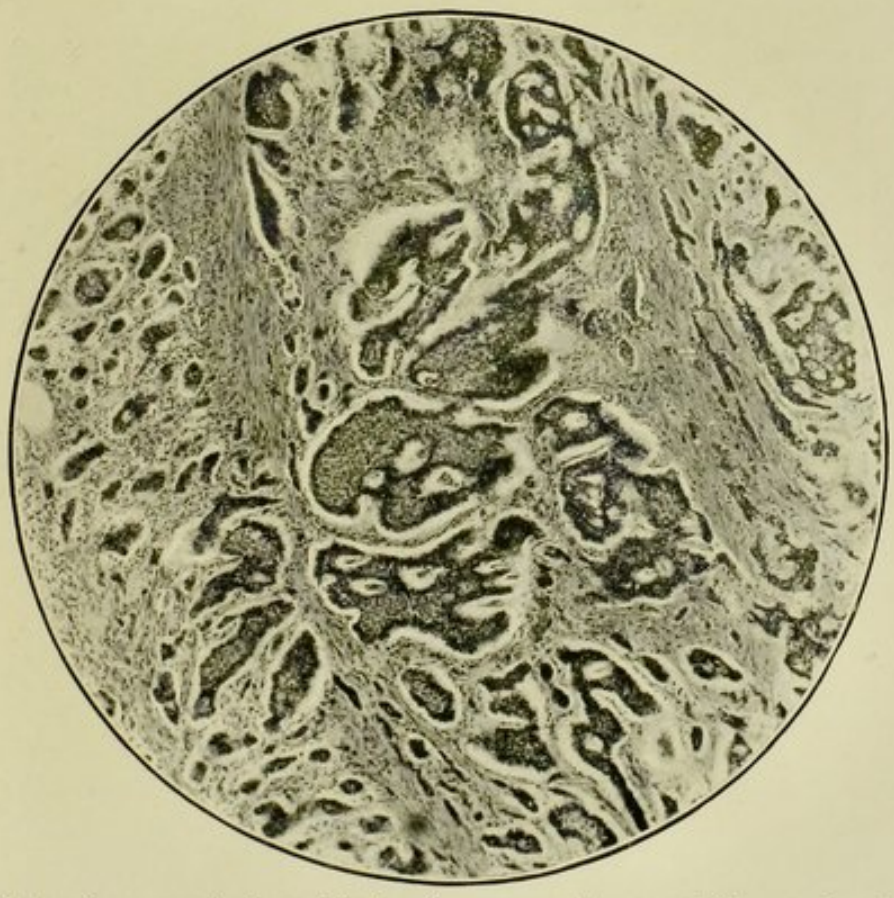
FIG. 1.



Photomicrograph of primary spheroidal-celled carcinoma of the vermiform appendix, showing vacuolation (Case xi). × 175. (Photomicrograph by Dr. H. Spitta.)

FIG. 2.



Photomicrograph of multiple primary carcinoma of ileum, showing vacuolation (C. H. Bunting, 'Johns Hopkins Hospital Bull.,' vol. xv, p. 389, 1904), from section kindly provided by Dr. Bunting. × 170. (Photomicrograph by Dr. H. Spitta.)

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