Observations

ON

THE RELATION OF MALIGNANT DISEASE
TO BENIGN TUMOURS OF THE
INTESTINAL TRACT.*

BY

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THE subject of our discussion is not new, but it is one to which considerable attention has been devoted in recent years, and it may be useful if, at this time, we endeavour to bring together such facts as we may think we have ascertained in the course of our labours, and such speculations as may help to give a clue to our obscurities. In particular it is desirable to know to what extent we are in agreement on the main issues, and wherein individual experience differs.

In going over the data, anatomical and documentary, which I have accumulated on this subject during the last twenty years, I have been surprised at both its amount and its variety. Simple tumours of the alimentary tract, like so many other unobtrusive lesions, are found with considerable frequency when carefully looked for, and, while usually of little clinical importance *per se*, in a certain proportion of cases they are attended by the most serious consequences. It is with one of these consequences, the development of malignancy, that we are concerned to-day.

As opener of the discussion it will probably be most convenient if I pass in review the various kinds of simple tumours which occur in the alimentary tract, considering at the same time the incidence and nature of the malignant changes to which each is liable. Subsequent speakers can then extend and elaborate those aspects of the problem in which they are particularly interested. My own remarks will be based chiefly on my personal experience of human material, but it is hoped that during the discussion the comparative and experimental sides will not be neglected.

CONNECTIVE TISSUE TUMOURS.

Simple connective tissue tumours of the alimentary tract are of comparatively infrequent occurrence, the only two of any consequence being lipoma and leiomyoma. I have encountered only five examples of submucous lipoma of the stomach, all of them small and sessile, mere casual findings at necropsy. In another case there was a pedunculated lipoma the size of a hazel-nut at the junction of the first and second portions of the duodenum. It also was a casual finding; but tumours of this type elsewhere in the intestines may be the starting-point of intussusception. Subserous lipomas are more common. They really arise in the mesenteric adipose tissue, are not infrequently multiple, and seldom attain a large size. Lipomas in general rarely undergo malignant change, and I am not aware that any case of the kind has been reported in connexion with the intestinal tract. Leiomyomas are much more common and occur chiefly in the stomach and oesophagus. They are most frequently met with casually in the post-mortem room as small, flat, sessile, button-like growths, measuring up to one inch in diameter and projecting slightly from the mucosal surface. This is due to the fact that they usually originate in the inner layer of the muscular coat and naturally project in the line of least resistance. These tumours grow slowly, and very rarely attain a large size. Of twenty-two cases of leiomyoma of the stomach which I have encountered, the largest was no bigger than a walnut. It was rounded, lobulated, and semi-pedunculated. In the museum there is shown a leiomyoma of the ileum fully two inches in diameter which had caused obstruction and which was successfully removed at operation. The cut surface shows the characteristic whorling of these growths. As with uterine fibroids, alimentary tract leiomyomas occasionally become sarcomatous. In the uterus it may be

possible to trace the sarcomatous change in one out of several fibroids present, but in the gut, where single tumours are the rule, considerable doubt may remain as to whether a spindle-cell leiomyosarcoma has originated in a simple myoma or has been malignant from the outset. In this connexion it may be mentioned that myosarcoma appears to be more frequent in the small intestine than in the stomach, whereas the reverse is the case with regard to myoma. Unstriated muscle tissue also enters into the composition of the so-called adenomyomas of the stomach and intestine, tumours which will be discussed later.

EPITHELIAL TUMOURS.

The simple epithelial tumours are undoubtedly the most important members of the group now under discussion, not only because they are dangerous in themselves as a cause of haemorrhage or obstruction or as the starting-point of intussusception, but also because they are with good reason suspect as precancerous lesions. In structure they are generally adenomatous, but a villous papilloma is also encountered, particularly in the rectum. Starting as small flat patches of glandular overgrowth, these tumours tend to become polypoidal at an early stage of their career, and in this form they may ultimately attain a considerable size, as much as one or two inches in diameter. They show a notable tendency to multiplicity, especially in the large intestine, and occasionally there may be several hundred present. The conversion of the tumour from a wholly sessile plaque to a pedunculated polypus is brought about chiefly by the muscular movements of the gut, aided, perhaps, by the action of gravity. The pedicle is often quite definitely composed, not of tumour tissue, but of pulled-out normal or much thinned mucosa—an important point in relation to the surgical treatment of solitary polyps. The muscularis mucosae is dragged inwards with the rest of the mucous membrane, and may show considerable increase in thickness. Its presence, unbreached by epithelium, is the best evidence that a polyp has not yet become malignant, although, as will be shown later, suspicious changes may already be visible in the mucosa. The fibrous tissue core of gastric polypi, on which Menetrier (1888) has laid stress as indicating a pre-existing gastritis, is probably rather a reactive thickening of the submucosa in response to the mechanical drag of the polyp. The relation of chronic gastritis to multiple polyps of the stomach—whence the term “gastritis polyposa”—has been emphasized by many writers, but it is difficult to account for solitary polypi in this way; yet the two lesions are indistinguishable microscopically, while chronic gastritis, without any suggestion of polyposis, is a common accompaniment of both ulcer and cancer of the stomach. In the colon the corresponding lesion, colitis polyposa, is sometimes familial. In its early stages Ewing (1928) finds that there is a diffuse and pronounced hypertrophy of the entire epithelial lining, which supports Versé's view that the sole element in the predisposition is the excessive reaction of the epithelium to irritants. Here again it is difficult to account for solitary polypi on an inflammatory hypothesis.

Relation of Adenoma to Carcinoma.

The connexion between simple adenomata of the intestine and carcinoma is now well established. Dukes (1925-26), who has investigated this question with great thoroughness, found that of 33 consecutive cases of carcinoma of the rectum and sigmoid operated on at St. Mark's Hospital no fewer than 25 showed the presence of adenomata. He considers that this figure—75 per cent.—is probably an underestimate, since only the surgical specimens were available for examination, and adenomata may have been present elsewhere in the intestine. I show in the museum several interesting examples of this association, including a case in which widespread polyposis was associated with two independent carcinomata, one in the rectum just above the anus, the other some ten inches higher up. As both Dr. Dukes and Dr. Susman are taking part in the discussion, I will leave them to deal in greater detail with this very important part of the subject.

So far as the stomach is concerned, opinion is hardening in the same direction. Cruveilhier (1835-42), who figures

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a beautiful example of multiple gastric polypi in his great atlas, expresses the opinion that malignant degeneration of polypi ought to be frequent, and thinks it possible that many of the cancerous vegetations of the pylorus or its neighbourhood which are met with not infrequently may have originated in this way. The cancerous evolution of gastric polyadenoma has been especially emphasized by Menetrier (1888; Menetrier and Clunet, 1907), and in recent years a number of writers have expressed a similar opinion. Thus Brunn and Pearl (1926) collected 84 cases of diffuse polyposis of the stomach, of which 10 (12 per cent.) were malignant, while in Mills's (1922-23) series carcinoma at or near the pylorus was present in 4 out of 20 cases (20 per cent.).

My own experience of gastric polypi, now a considerable one, affords further evidence of the sinister significance of these ostensibly harmless growths. In the course of 11,000 necropsies performed at the Leeds General Infirmary during the last nineteen years (1910-28) there were 47 cases (0.43 per cent.) in which gastric polypi were present—namely, 27 with single polypi, 7 with two, 1 with three, and 2 with four, while in 10 cases there were numerous polypi. The same series of necropsies included 263 cases of carcinoma of the stomach. The association of the two lesions is shown in the following table.

Polypi and Cancer of Stomach.

	No. of cases with polypi.	No. associated with carcinoma.	Percentage of cases of polypi with carcinoma.
Single	27	6	22
Multiple	20	7	35
	47	13	28

Looked at from the opposite standpoint, 13 out of 263 cases of carcinoma of the stomach (4.9 per cent.) were associated with polypi. This is approximately one-third the frequency (15.7 per cent.) with which, in my clinical series, carcinoma originated in relation to simple chronic ulcer. The contrast with Duke's figure for carcinoma and polypi of the rectum and colon (75 per cent.) is remarkable.

In two other cases a single simple polypus of the stomach was associated with carcinoma of the colon. In three cases only was it possible to say with certainty that the carcinomatous change had originated in a polyp. In the others such an origin could not be excluded, although in certain of them the polypi were some little distance from the malignant growth. Six of our cases are shown in the museum. Two of these, which have already been published in abstract in the *Proceedings of the Pathological Society of Great Britain and Ireland* (Stewart, 1913-14, Gleave, 1923), are beautiful examples of multiple polyposis with carcinoma. A third case, which has been reproduced in the *Atlas of Pathological Anatomy of the British Journal of Surgery* (Fasciculus II, pp. 130-133), is of particular interest in that a large gastric polypus was found at operation together with a number of small sessile polypi. Partial gastrectomy was performed, from which the patient made a good recovery; but five weeks later she died rather suddenly and quite unexpectedly. At necropsy an unsuspected carcinoma at the cardia was disclosed, together with extensive secondary deposits in the liver and regional lymph glands.

Simple adenomatous polypi of the stomach, whether single or multiple, must therefore be accepted as a definitely precancerous lesion, but the available evidence goes to show that the association is much less intimate than in the case of the large intestine. In both sites one can occasionally trace the sequence of events with the microscope; more often this cannot be done. Usually malignancy develops at one point only, as in experimental tar cancer of the skin, but exceptions to this rule are not infrequent. Lockhart-Mummery and Dukes (1928) believe that with the progressive enlargement and dissemination of the malignant tumour there is accompanying retrogression of the hyperplastic changes and benign tumours surrounding the growth. Sometimes the pedicle of the polyp becomes so attenuated that the latter breaks off and is discharged per rectum (Ewing, loc. cit.).

Criteria of Early Malignancy in Gastro-intestinal Polypi.

It is not always possible to say definitely that a given polypoidal tumour of the stomach or intestine is malignant. The most important criterion is epithelial invasion of the muscularis mucosae, especially if this is associated with atypical cellular characters—cellular and nuclear heteromorphism, nuclear hyperchromatism, and the formation of solid epithelial masses or irregular acini. There is very little risk of confounding the obviously simple heterotopic tumours, deep in the wall of the gut, with malignant penetration. The chief difficulty arises in connexion with tumours where the muscularis mucosae has not been penetrated, but in which irregular cellular characters and de-differentiation of epithelium are present. These changes are frequent in both gastric and intestinal polypi, and while one cannot say that they certainly indicate the commencement of malignancy, they must be viewed with grave suspicion. In cases of this kind the examination of further sections from the same or another block will sometimes reveal early penetration of the muscularis mucosae.

ADENOMYOMA AND PANCREATIC HETEROTOPIA.

These closely related lesions occur in the stomach, duodenum, and small intestine, the former as something of a rarity, the latter with comparative frequency. In a consecutive series of 5,700 post-mortem examinations at Leeds there were 7 examples of adenomyoma and 22 of pancreatic heterotopia, distributed as follows:

	Adenomyoma.	Heterotopic pancreas.
Stomach	4	4
Duodenum	0	15
Small intestine	2	1
Meckel's diverticulum	1	2

A. L. Taylor and I have already described these formations in detail (Stewart and Taylor, 1925; Taylor, 1927), and it need only be said here that there is no evidence that either of them is specially liable to malignant transformation. Only three examples of pancreatic carcinoma arising in the stomach or intestine have been described (Herxheimer, 1913; Seidelin, 1912-13; and Nicholson, 1923), yet, as the above figures show, pancreatic heterotopia in these situations is of fairly frequent occurrence. I have no knowledge of a carcinoma arising in a pre-existing adenomyoma.

CARCINOID TUMOURS.

The carcinoid tumour of the appendix and small intestine, like rodent ulcer of the skin, occupies an intermediate position between the simple and the malignant tumours. It is locally infiltrative, very slowly growing, and, in the appendix, eminently amenable to surgical treatment. In rare instances dissemination to the regional lymph glands or even to the liver may occur. Taylor and I (1926), in a careful search of the literature, found only 18 published cases. This event, when it occurs, must be regarded as part of the natural history of the disease; there is no evidence that these tumours undergo a malignant metamorphosis of the kind we are considering to-day.

EXPERIMENTAL PATHOLOGY.

From the experimental side there is little to report directly bearing on this subject. Fibiger's (1913, 1914) classical experiments in the production of gastric carcinoma by feeding with *Gongylonema neoplasticum* may be mentioned, since the definite sequence of chronic inflammation, papillomatosis, and cancer was produced. These changes, however, are not strictly comparable with those occurring in man, inasmuch as they are confined in their origin to that portion of the stomach which is lined by squamous epithelium. Curiously enough, one of Fibiger's rats had a large pedunculated adenopapilloma of the colon, but as this was entirely free from parasites it was presumably an independent formation.

Bullock and Rohdenburg (1918) carried out a series of experiments in rats by introducing into the stomach mechanical and chemical irritants, the former consisting of celluloid balls covered with bristles and cork balls armed with pin-points, the latter of scharlach R and pine-tar,

either applied directly to the gastric epithelium or injected into the wall of the organ after gastrotomy. Extensive epithelial proliferative changes and even a certain amount of infiltration followed, but in no case did they succeed in producing a lesion which they were prepared to accept as carcinomatous. In the glandular region of the stomach the lesions resembled cystadenomata.

Ishibashi and Otani (1921) introduced 0.5 c.cm. of coal-tar into the submucosa of the stomach and intestine in rabbits, and two weeks later found in the stomach papillary adenomas, which, after fifty days, had shown no evidences of regression. In the intestine there was only a slight hyperplasia, with no sign of adenomatous proliferation.

Leitch (1923) injected tar per rectum in rabbits three times a week for over eight months without producing any evident tumour formation in the rectal mucosa, although in several cases papillomata formed on the skin outside the anus. Experiments in rats were equally unsuccessful.

Menetrier (1924; Menetrier and Derville, 1924), on the other hand, succeeded in producing an infiltrating squamous carcinoma of the cardiac end of the stomach of a rat by a series of tar injections into the left perirenal region followed by a series of oil of cade injections at the same site, the whole extending over a period of eleven months. Death followed the introduction of 3 or 4 drops of pure creosote. At necropsy a squamous carcinoma of the stomach was found in immediate relation to the injected tar, all of which, however, lay outside the gastric wall. The usual sequence of changes appeared to have taken place—inflammatory reaction, hyperplasia, papillomatosis, cancer.

Schabad (1926) administered tar by the mouth and per rectum to white mice, with negative results. In the stomach there resulted only thickening and keratosis of the mucosa; in the rectum, necrosis, inflammatory changes, and cicatrization. The changes in the perianal skin, however, were those of an epithelial new growth of canceroid type.

CONCLUSIONS.

1. An important and intimate relationship exists, both in the stomach and in the rectum and colon, between simple adenomatous polypi and carcinoma.

2. The evidence goes to show that an actual malignant metamorphosis takes place in the epithelium of one or more of the polyps, although the ultimate full development of malignancy is in most cases confined to a single focus.

3. As a local factor in the etiology of cancer, intestinal polypi occupy a most important position, much more so than their gastric congeners.

4. In cases in which a single polypus only is present simple removal of the tumour with its pedicle and base may be followed by cure, even after definite carcinomatous change has occurred. In cases of generalized polyposis only extensive operative procedures with a high mortality—gastrectomy, total or partial, or colectomy—are likely to be successful in preventing the onset or checking the spread of malignancy.

5. There is a certain amount of evidence to show that sarcomatous metamorphosis may occasionally occur in simple leiomyomatous tumours of the alimentary tract, just as in uterine fibroids.

6. There is no evidence that the simple heterotopic tumours of the stomach and intestines—adenomyoma, pancreatic heterotopia, Brunnerian adenoma—are specially liable to malignant change.

7. The so-called carcinoid tumours of the appendix and small intestine very rarely undergo metastasis to lymph glands or liver. This, when it occurs, is part of the natural history of these tumours (cf. rodent ulcer of the skin), and does not indicate anything in the nature of a new or superimposed malignancy.

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DIVERTICULITIS.*

BY

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DIVERTICULITIS of the sigmoid colon has long been known to pathologists by various names, but until recent times was looked upon as a rare disease. We know now that it is not rare, but it still receives less space in the textbooks than is given to disorders that are seldom met with and do much less harm.

It is just thirty years since a paper by Graser appeared, in 1898. This author, as far as I know, was the first to suggest that the frequency of inflammation of the peritoneum about the sigmoid colon is due to diverticula. He also made microscopic studies showing the frequency of diverticula in adults. In America, Fischer (1900), Beer (1904), Gordinier and Sampson (1906), and others published valuable studies. Special mention must be made of the paper of Mayo, Wilson, and Giffin which appeared in 1907. In this country Moynihan (1907) and Telling (1908) led the way. Dr. Telling's later paper, with Gruner, is a compendium of pre-x-ray studies, full of observation, reading, and reasoning. In France, the papers of Patel (1911) and of Bensaude, Cain, and Hillemand (1913) should be mentioned.

When x rays began to be applied to the study of diseases of the bowel a flood of new light was shed upon this as upon many other disorders. For more can be learned about the function and lumen of the bowel in a case of diverticulitis by a combined clinical and good x-ray examination than by a laparotomy or a post-mortem inspection. It soon appeared that whilst sigmoid diverticulitis was not infrequent, a precedent condition of the bowel in which diverticula were present along the colon, but not inflamed, was often found and was not associated with any clinical state that could be called diverticulitis. We had observed a series of these cases before 1920, and it was proposed to give them the name of diverticulosis. Soon afterwards my colleague O. A. Marxer, upon whose studies what I have to say from a radiological point of view is founded, detected a still earlier stage of the disorder, the pre-diverticular state.

There are, therefore, three main stages in the progress of the disease:

1. The pre-diverticular state
2. The stage of formed diverticula
3. The stage of inflamed diverticula, or diverticulitis.

We have many times observed each of these stages pass into the next. They may all be present at once at different parts of the bowel, or even in the same segment.

Although it is only the last stage which has surgical implications and is to be discussed to-day, yet something should be said about the earlier ones; indeed, they fall logically under the headings of the etiology and of the possible prevention of diverticulitis.

The pre-diverticular state was first described fully at the Clinical Society of this city in 1925. It had been briefly referred to in print by O. A. Marxer two years earlier, and was first recognized in 1920. The part of the bowel affected loses its normal segmentation and

* Read in opening a discussion in the Section of Surgery at the Annual Meeting of the British Medical Association, Manchester, 1929.