# Metastasizing Carcinoma of the Stomach in Peutz-Jeghers Syndrome

BENJAMIN A. PAYSON,* M.D., BASIL MOUMGIS,** M.D.

*From the Surgery and Pathology Services, Beekman-Downtown Hospital, New York, New York*

THE PEUTZ-JEGHERS SYNDROME,[7, 9] characterized by pigmentation of the skin and mucous membranes and gastro-intestinal polyposis, has been well documented since the original description in 1921. The familial tendency (as a simple Mendelian dominant) and the tendency to intussusception are well established. There have been conflicting views, however, as to the frequency with which malignant change occurs in the polyp. In a number of instances malignant changes have been reported, but a review of the literature indicates that the diagnosis is based solely on histologic changes within the polyp. Until 1963, no case of metastases to regional lymph nodes or death had been reported.

The case here described is an exceptional instance of carcinoma of the stomach with lymph node metastases associated with the Peutz-Jeghers syndrome.

## Case Report

A 21-year-old dark-skinned Puerto Rican was admitted to Beekman-Downtown Hospital on November 28, 1965, because of frequent passage of bright red blood per rectum for the last 2 years. He had never sought medical attention. In the recent 2 months, however, he lost weight, his appetite became poor and he tired easily. He complained of occasional nausea and vomited some brownish material shortly before admission. He is an only child of divorced parents. Both parents remarried and to his knowledge neither his parents nor half-brothers and sisters have been hospitalized or treated for any serious illness. He is the sole member of the family to migrate to the United States. The others are living *somewhere* in Puerto Rico and unavailable for interview or examination.

He recalled that as a child he suffered from intermittent abdominal cramps and on one occasion a small lump protruded from his anus, caused some bleeding but he was able to "push it back." He was always aware of *birth marks* on his lips and hands.

He appeared undernourished, poorly developed and much younger than his stated age. Facial hair was sparse. The sclerae were pale. On the inner aspect of the lips and buccal cavity there were 2 to 5 mm. scattered flat brown pigmented spots (Fig. 1). Similar lesions were seen on the volar aspect of the fingers of both hands and a few scattered on the plantar surface of the toes and feet. The lungs were clear. The abdomen was flat, soft and not tender. No masses were palpable. Rectal examination revealed multiple soft polyps which were freely movable and bled easily.

*Laboratory Data.* Hemoglobin was 7.4 Gm., hematocrit 26%, WBC 9,250. Urinalysis was normal. Prothrombin time 13.0 sec. Fasting Blood Sugar 90 mg.%, BUN 15 mg.%. Alkaline phosphatase 3.2 units. Total protein 7.2 Gm.%. Gastric analysis: Free HCL 34.9 degrees. Combined acid 50.0 degrees, Guiaic positive.

On sigmoidoscopy to 10 inches multiple small polypoid masses varying from a few mm. to 2 cm. were seen. Large ones were pedunculated and smaller ones were flat, resembling mucosal excrescences. These lesions extended from the anus to the distal end of the scope. A biopsy specimen was taken from one of the larger rectal polyps (Fig. 2).

Barium and air contrast enema x-rays showed multiple polyps throughout the colon, the largest measuring 3 cm. (Fig. 3). Gastro-intestinal x-ray series showed a large filling defect in the antrum of the stomach thought to be an annular carcinoma (Fig. 4). In addition, polyps were seen in

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* Attending Surgeon, Beekman-Downtown Hospital.

** Assistant Attending Pathologist, Beekman-Downtown Hospital.

the duodenum and upper jejunum. There were also dilated loops of small bowel in the upper abdomen.

*Hospital Course.* The patient was uncomplaining while investigation was in progress. Operation December 7, 1965, disclosed the following: Immediately on entering the peritoneal cavity a double intussusception of jejunum with obvious chronic obstruction was seen (Fig. 5a, b). The intussuscepted bowel was distended and thickened and within the intussusception two polypoid masses could be palpated. Distal to the intussusception the small bowel was collapsed. In the hepatic flexure, transverse colon, descending colon and sigmoid many large and small polyps could be palpated. A polyp was likewise found in the second portion of the duodenum. Within the pyloric region of the stomach there was a $4 \times 5$ cm. hard mass extending from the antrum down to and including the first portion of the duodenum. There was a conglomeration of large, firm nodes in the infrapyloric region of the stomach. The diagnosis was carcinoma of the distal portion of the stomach with lymph node metastases. The liver was free of palpable metastases and there was no evidence of metastases to the omentum and parietes. A 75% subtotal gastrectomy and omentectomy was performed and the jejunal intussusception was reduced. The two large jejunal polyps about 5 inches distal to the ligament of Treitz were excised and the opening in the jejunum was utilized for the gastrojejunostomy. One polyp measured $4 \times 4$ cm. and the larger one $6 \times 6$ cm. The postoperative course was uneventful, and he was discharged on the 14th postoperative day. The rectal polyps were subsequently treated by electrocoagulation.

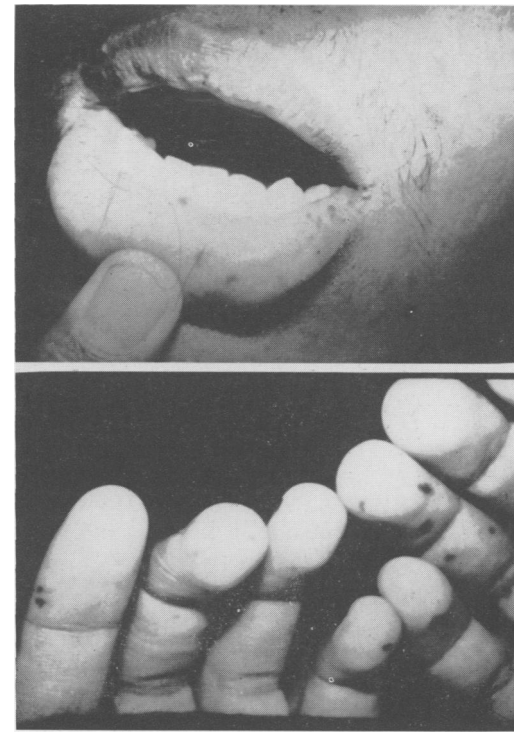

FIG. 1. Scattered flat melanotic spots on the lips and volar aspect of the fingers.

*Pathology.* In the resected gastroduodenal specimen there was a large (5 cm.) infiltrating

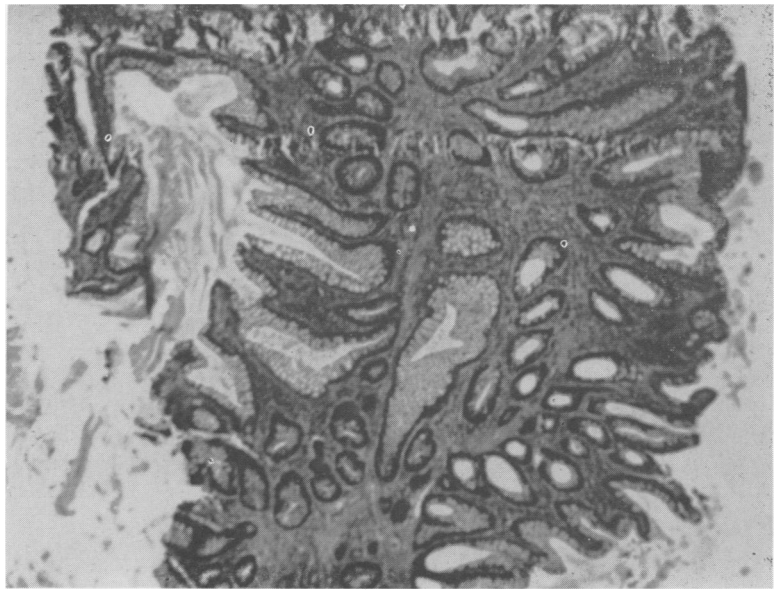

FIG. 2. Biopsy of rectal polyp revealing glands interspersed with smooth muscle bundles simulating invasion and indicating hamartomatous nature of polyp (×35).

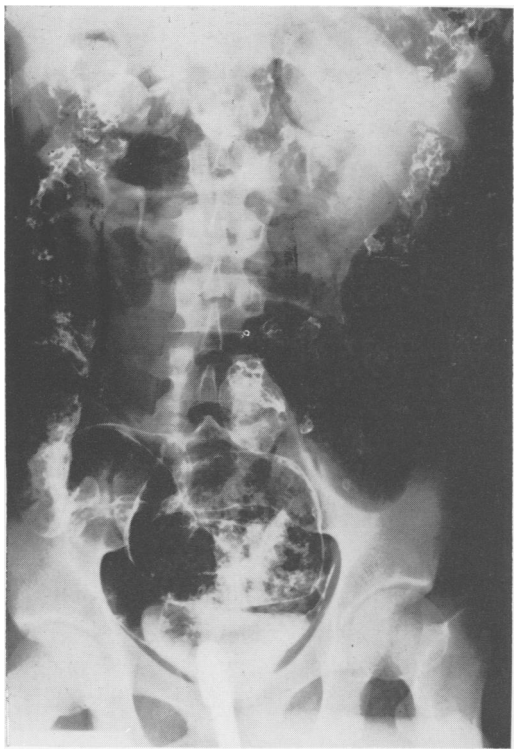

FIG. 3. Air contrast study of the colon delineating multiple polyps throughout the bowel. Note the large polyps in the hepatic flexure.

annular partially obstructing neoplastic mass involving the gastric antrum, pylorus and proximal duodenum. Internally, the mass was about 6 cm. long and had a large central area of necrosis and ulceration with gross infiltration of the wall (Fig. 6). There was a matted subpyloric mass of large lymph nodes. Microscopically, the neoplasm was composed of pleomorphic, polychromatic cells with little evidence of histoid pattern. There were, however, some areas of glandular pattern (Fig. 7) and in places the cells were arranged in sheets and large nests in a medullary pattern. Paneth cells were seen and many lymphatic channels contained neoplastic cells. The large subantral lymph nodes were replaced by neoplastic tissue (Fig. 8). Metastatic deposits were present in several small lymph nodes along both the greater and lesser curvatures of the stomach and in lymphatic channels in adipose tissue adjacent to the nodes. The *uninvolved* gastric mucosa revealed many small polypoid mucosal excrescences up to 0.8 cm. in diameter which were grossly and microscopically confined to the mucosa and showed large distorted and dilated glands but no histologic evidence of malignant invasion.

The jejunal polyps measured 6 and 4 cm. in greatest dimension and had nodular cauliflower-like surfaces. Microscopically, there were large polypoid masses of glands arranged in haphazard pattern intermingled with bundles of smooth muscle of varying size (Fig. 9). Many glands were dilated and cystic. There was mild pleomorphism of cells but no histologic evidence of carcinoma. Mitotic figures were absent.

Three rectal masses had polypoid mucosa with glandular dilatation and slight distortion. The epithelial cells showed no evidence of carcinoma. Glands were seen interspersed with smooth muscle bundles simulating invasion and indicating the hamartomatous nature of the *polyp*.

## Discussion

In the years since the Peutz-Jeghers syndrome was first described, there has been considerable discussion and conjecture concerning the malignant potential of the polyps. The histologic structure, characterized by epithelial elements with considerable mitotic activity (normally present in

FIG. 4. Roentgenogram of the stomach. There is a filling defect in the antrum with rigidity of the wall. Note outline of a polyp in the transverse colon by residual barium.

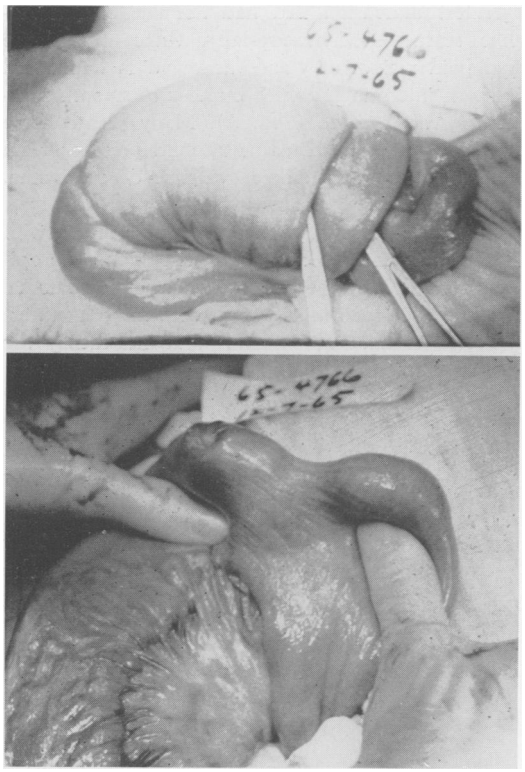

FIG. 5. (top) Double intussusception of the jejunum with proximal distention and distal collapse of the bowel. (bottom) After reduction two large polyps are disclosed.

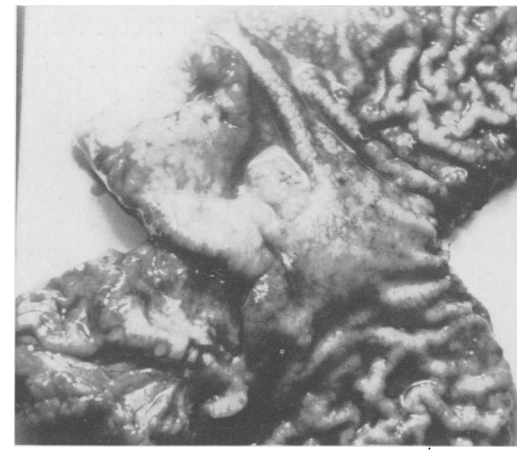

FIG. 6. Resected gastric specimen revealing ulcerated carcinoma at the pylorus. Note multiple small polypoid excrescences scattered throughout gastric mucosa.

small bowel mucosa) interspersed by bands of smooth muscle, has mistakenly been interpreted as invasion, and the incidence of carcinoma was thought to be high. These interpretations were based on microscopic changes alone and not on evidence of lymphatic invasion or distant metastases. Bailey,[2] in 1957, reported a total incidence of carcinoma in 24% of 67 reported cases.

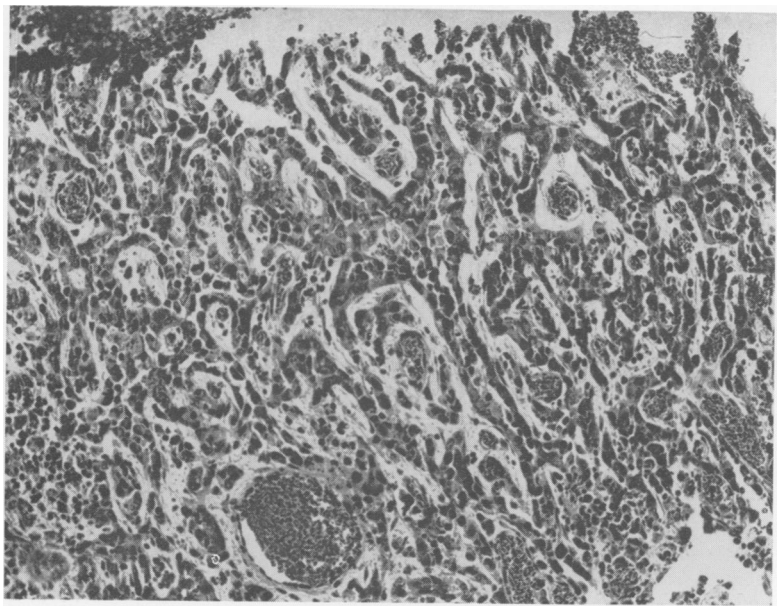

FIG. 7. Microphotograph of carcinoma of the stomach revealing glandular pattern (×150).

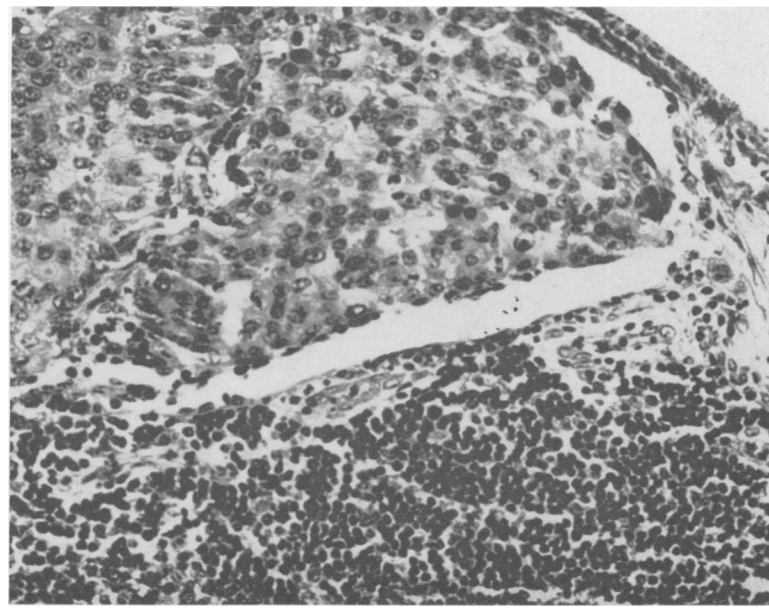

FIG. 8. Microphotograph of perigastric lymph node revealing metastatic carcinoma-undifferentiated pattern (×150).

Bartholomew [3] was the first to interpret the pathologic change as congenital malformation or hamartoma, and the present concept that the polyps in the Peutz-Jeghers syndrome are essentially benign is based on his interpretation. Dormandy,[5] in a review of 21 patients in five families, concluded that true malignant degeneration rarely occurs. He agrees that the presence of adenomatous elements in the deeper layers of the bowel wall may give rise to deceptive microscopic appearances. Burdick [4] reviewed a family group of ten patients with this syndrome and followed them for a 10-year period. All failed to develop malignant changes.

Williams and Knudsen [11] described the first example of carcinomatous changes in a duodenal polyp in the Peutz-Jeghers syndrome, a metastasis having occurred in a regional lymph node. The patient died of cachexia 15 months after operation. They warn that the borderline between hamartomatous malformation and *true tumor* is by no means distinct.

In 1963, Horn *et al.*[6] reported what they thought to be the first case of Peutz-Jeghers syndrome which terminated fatally with metastases from a gastroduodenal carcinoma. The patient was initially recognized to have the syndrome at 12 years of age and 33 years later, at operation for intestinal obstruction, a diagnosis of carcinoma of the stomach with liver metastases was made and proved at autopsy soon afterward. Polyps were found in the stomach and duodenum with 50 others scattered throughout the remaining gastro-intestinal tract down to the anus. That same year, Achord and Proctor [1] reported their *first case* of malignant degeneration with metastases in a 13-year-old girl with pigmentation, polyposis of the small and large bowel, and a filling defect in the stomach. The child died a few months after the diagnosis was established and autopsy showed extensive carcinoma of the stomach with ascites and liver metastases. In 1965, Reid [10] reported a case of a 39-year-old woman who died from a carcinoma of the duodenum with lymph node and myocardial metastases.

Yoshida *et al.*,[12] in a review of the Japanese literature, reported a case of Peutz-Jeghers syndrome with definite evidence of mitotic figures in the mucosa and infiltrat-

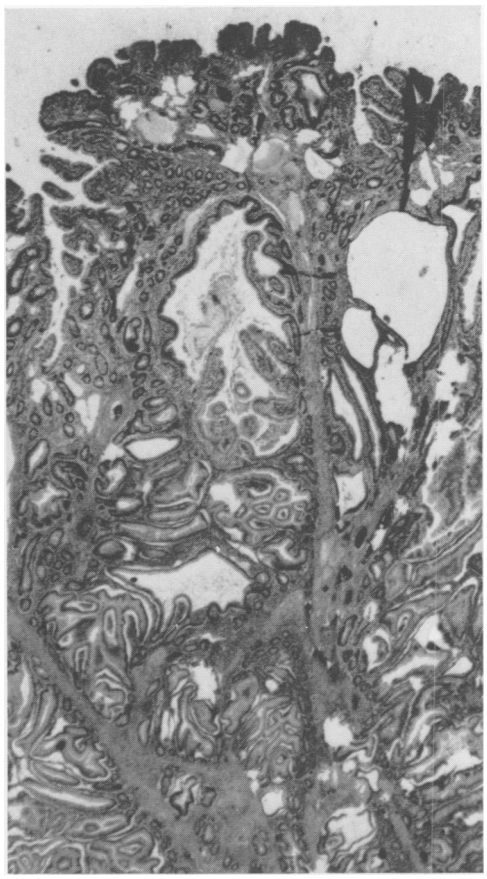

FIG. 9. Microphotograph of a jejunal polyp revealing masses of glands intermingled with bundles of smooth muscle (hamartoma) and mild pleomorphism, but no histologic evidence of malignancy (×35).

ing carcinoma into the stalk of a gastric polyp. The report of Williams and Knudsen [11] with regional lymph node metastases from duodenal carcinoma, is the only case in which there seems to be unequivocal evidence of carcinoma arising in a polyp.

Accumulating case reports of carcinoma in the stomach and duodenum in association with the Peutz-Jeghers syndrome lead to the conclusion that the syndrome cannot be dismissed as completely benign. It is conceded that, to the present at least, there has been no evidence that polyps in the small bowel distal to the ligament of Treitz undergo malignant change or are associated with malignant lesions. It seems, however, that the several instances of carcinoma of the gastroduodenal regions indicates more than a fortuitous association especially considering the early age at which these lesions appeared.

As far as the colon is concerned, there has been no evidence of an increased incidence of rectal or colonic carcinoma. Morson [8] could find no example in the extensive records of St. Mark's Hospital collected over 30 years.

## Summary

There have been conflicting views as to the frequency with which malignant change occurs in the polyps associated with the Peutz-Jeghers syndrome. This has been due to the difficulty in interpreting the histologic structure of the polyp. There has been agreement that the lesions are hamartomas and benign. There has been no case reported of unequivocal metastases from a carcinoma of the small or large intestine associated with the syndrome.

The case described and recent reports of metastasizing carcinoma in the stomach and duodenum associated with the Peutz-Jeghers syndrome lead to the conclusion that at least in these areas the syndrome cannot be dismissed as completely benign.

## Acknowledgment

The authors are indebted to Dr. Hiromi Shinya for translating the publication by Yoshida *et al.*

## Addendum

Since the manuscript was submitted for publication, the patient was re-admitted to Memorial Hospital, New York City, where he died on September 25, 1966. Autopsy showed ascites, extrahepatic biliary obstruction secondary to massive recurred carcinoma involving the porta hepatis, head and body of the pancreas and bilateral lung metastases.

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